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THE DANGERS OF ANTIBIOTICS.[1]

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THE discovery of antibiotics has revolutionized medical practice. Not only have they been brilliantly successful in the cure of hitherto incurable diseases, but the toxicity of antibiotics used in therapy is much less than that of arsenicals and sulphonamides.

Nevertheless there are dangers associated with the accepted antibiotics and it is time we began to consider them. These dangers are due to three causes: (i) side effects, (ii) unwise use of antibiotics, (iii) resistant organisms. The possible side effects are toxic or allergic manifestations and the substitution of a new pathogen (superinfection).

Toxic effects of the antibiotics in clinical use are rare. Aplastic anæmia due to streptomycin has been reported on three occasions; chloramphenicol may produce anæmia and severe leucopenia. It is well known that streptomycin in prolonged use causes damage to the vestibular apparatus; but with a dose of one gramme every three days this will very rarely happen. The hope that dihydrostreptomycin would be much less toxic proved ill founded, and extensive use has revealed that though it rarely causes vestibular damage, it may lead to the insidious onset of progressive and permanent deafness (Don, 1952) and its use should be discontinued.

[1] Read at a meeting of the New South Wales Branch of the British Medical Association on April 24, 1952.

Allergy to penicillin is not rare, and urticaria is the commonest manifestation. Exfoliative dermatitis has occurred. Two cases have been reported of severe anaphylaxis following instillation of penicillin into the antrum (Everett, 1951).

Topical application has often a powerful sensitizing effect.

A well-known member of our profession used penicillin lozenges to treat his pharyngitis. Some months later he suffered a septic infection of a finger, for which an injection of penicillin was given. Within a few minutes his lips and tongue became greatly swollen, and as well as being very uncomfortable, he suffered considerable apprehension lest a tracheotomy be needed. Fortunately the swelling soon subsided.

Stomatitis is said to occur in about 6% of persons who use penicillin aerosol therapy. Occasionally penicillin has produced asthma. A more rare effect is the occurrence of fever without other signs of allergy.

Another undesirable side effect of antibiotics, especially when used for more than a week, consists in the substitution for the original infection of another pathogen previously present somewhere in the body as a saprophyte. This is frequently a fungus (*Candida albicans* or Aspergillus), coliform bacillus, *Bacillus proteus* or *Bacillus pyocyaneus* or a staphylococcus, which inhabits the lower part of the alimentary tract.

The gastro-intestinal effects of some antibiotics are important and intensely interesting except to those who suffer them. They occur mostly with aureomycin, chloramphenicol or terramycin, and consist in perianal irritation, diarrhœa (which may continue for weeks), sore mouth and tongue, nausea and epigastric discomfort. These

are considered largely due to Monilia (Candida) infection; but vitamin *B* group deficiency plays a part and so does the sex of the patient. In one series of 110 patients, two-thirds of the women and one-fifth of the males developed gastro-intestinal symptoms. The females often had anal and vulval irritation and a vesiculo-papular eruption in the mouth. With large doses of vitamin *B* group the reactions were less severe. Sour milk and lactose have been suggested to hasten the reestablishment of normal intestinal flora.

In *The Journal of the American Medical Association*, of April 21, 1951, appears the following announcement by the Council on Pharmacy and Chemistry that a warning should be included on the labels of aureomycin, chloramphenicol and terramycin.

> The new antibiotics Chloramphenicol, Aureomycin Hydrochloride and Terramycin Hydrochloride are highly bacteriostatic for many bacteria. Susceptible bacteria are suppressed and Monilia and other yeast-like organisms may replace the normal or abnormal bacterial flora. This most frequently occurs in the large bowel and is of little consequence. However, if this replacement occurs in a lung abscess, bronchiectatic cavity or in certain other lesions, a condition is created which may be unfavourable for the patient. Deaths from pulmonary moniliasis following therapy with the new antibiotics are known. Also instances of cutaneous moniliasis mistaken for sensitivity have been noted when the newer antibiotics were used in the treatment of disease.

Fatal endocarditis due to Aspergillus following prolonged use of penicillin has been reported by Zimmerman (1950), and fatal pulmonary cavitating aspergillosis is described by Abbott (1952).

Superinfection is frequent when antibiotics are unwisely used in urinary infections. If there is interference with urinary flow with infection, which is treated by antibiotics without appropriate surgical measures, substitution of Proteus or Pyocyaneus is highly probable. When the new organism splits urea to ammonia it may lead to serious consequences.

Having considered briefly the undesirable side effects of antibiotics, we come now to what I believe is a more important result of their use. This is the tendency to treatment without diagnosis, to carelessness in aseptic precautions and to the unintelligent use of antibiotics.

There is a great temptation when one is dealing with a case of obscure fever to give antibiotics at once. When a person is dangerously ill this may be justified; but in most cases it is not and it may even be harmful.

A wealthy citizen developed a fever which failed to respond to sulphonamide. At the time virus pneumonia was a fashionable diagnosis and, being kept abreast of medical progress by a popular literary "digest", he knew that aureomycin was the remedy; its scarcity and cost merely whetted his appetite and soon he possessed a supply and insisted on taking it. The results were most gratifying; the fever disappeared and he appeared well. Unfortunately in a couple of weeks symptoms returned, but rapidly disappeared when the treatment was repeated, only to return a few weeks later. Finally, a considerable time after the onset, systematic investigation was undertaken, a diagnosis of subacute bacterial endocarditis was established and a cure was effected by penicillin.

Antibiotics are frequently used unwisely. H. A. Reimann (1952) gives the opinion that "90% of antibiotics as now administered (in U.S.A.) are wasted in overdosage and in the treatment of diseases not affected by them".

There is some experimental evidence that penicillin may increase the mortality in typhoid and stimulate tuberculous infection. Penicillin treatment is often blindly continued when it is obviously doing no good.

Frequently several antibiotics are prescribed simultaneously and may interfere with each other's action. Lepper and Dowling (1951) treated with penicillin 14 patients suffering from pneumococcal meningitis; all but three recovered. At the same time 14 similar patients were given aureomycin as well as penicillin; 11 died.

At the present time the only justifiable combination is that of penicillin and streptomycin in the treatment of certain penicillin-resistant organisms such as enterococcus. Resistance of various organisms to streptomycin develops in as little as one day, and in non-tuberculous infections there is therefore no point in using it for more than five days or in giving second courses.

The final danger of antibiotics lies in the development of resistant strains. There is more than a possibility that the increased incidence of these strains may in a few years render our antibiotics useless. Those of you who began practice before 1945 will realize only too acutely the calamity this would be. Anything we can do to retard this process is vitally important. For this paramount reason we should use antibiotics sparingly and wisely, as far as possible knowing the organism we wish to destroy, hitting it hard and stopping as soon as the job is done. Streptomycin in tuberculosis should not be used without PAS. Inadequate therapy, such as the use of penicillin lozenges, should be banned. "Shot-gun" treatment should be avoided; at present it is not uncommon.

> At the conclusion of an operation the surgeon said: "Put him on antibiotics." His assistant asked: "Which ones, sir?", to which came the reply: "All of them."

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THE DANGERS OF ANTIBIOTICS.[1]

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THE dangers arising from the use of antibiotics may be divided into two main groups: (i) toxic reactions which may follow the administration of an antibiotic to some subjects; (ii) alteration in the bacterial flora of the infective process, manifest either by the appearance of antibiotic-resistant strains of the infecting organism or by the appearance of other organisms which have not at any time shown sensitivity to any antibiotic.

It is intended in this communication to discuss only alteration in the bacterial flora.

The Development of Antibiotic-resistant Strains of the Infecting Organism.

That organisms can and do develop resistance to agents with which they come in contact is well known and has been shown, for example, in the development of resistance to sulphonamides and to some antiseptics. Although it was not realized at first that antibiotic-resistant strains of previously sensitive organisms could develop, this fact is now well known and well established. The incidence of antibiotic-resistant strains in hospital communities has reached an alarming level and presents a very difficult problem in relation to the treatment of patients and the control of cross-infection. It may well be that the indis-

[1] Read at a meeting of the New South Wales Branch of the British Medical Association on April 24, 1952.

TABLE I.

Incidence of Penicillin-Resistant Staphylococcus Pyogenes.

Author.	Place.	Date.	Source of Strains.	Number Examined.	Percentage of Resistant Strains.
North and Christie.	Australia.	1945		88	Nil
Barber.	London.	1946	Hospital patients	200	14·1
Barber.	London.	1947	Hospital patients	100	38
Barber.	London.	1948	Hospital patients	100	59
Barber and Whitehead.	London.	1949	Hospital patients	100	35
Martyn.	Manchester.	1949	Infants:		
			Nose	81	55·5
			Fæces	65	58·5
Forbes.	Kent.	1949	In-patients	38	68·4
			Out-patients	40	12·5
Rountree and Thomson.	Sydney.	1949	Hospital patients	196	53
Rountree, Barbour and Thomson.	Sydney.	1949	In-patients	513	53·4
		1950	Out-patients	90	24·6
Buckle.	Melbourne.	1949	Hospital patients	134	54
		1950			

criminate use of antibiotics has been an important contributing factor to the present high incidence of these antibiotic-resistant strains.

It is fortunate that the problem of antibiotic-resistant strains does not arise with all organisms; but recent work has shown that, even in the case of organisms which have been regarded as free from antibiotic resistance, some resistant strains are now beginning to appear. The *Streptococcus pyogenes* has not shown antibiotic resistance until recently, when a few resistant strains have been found; but as yet there is no problem in relation to resistant strains of this organism. The position with *Streptococcus pneumoniæ* is similar to that with *Streptococcus pyogenes*. The Gram-negative diplococci—*Neisseria gonorrhœæ* and *Neisseria meningitidis*—still remain antibiotic-sensitive, although resistant strains can be developed *in vitro*. The pathogenic Gram-positive bacilli are generally sensitive, although some penicillin-resistant strains of *Clostridium welchii* have been found.

The development of antibiotic-resistant strains of *Staphylococcus pyogenes*, of *Bacterium coli* and related Gram-negative bacilli, of *Proteus vulgaris* and of *Pseudomonas pyocyanea* presents the greatest problem, as the rapidly increasing number of strains of these organisms resistant to one or other or all of the antibiotics is being discovered.

Resistance of strains of *Mycobacterium tuberculosis* to streptomycin is well known.

It is not intended to discuss in detail the mechanism of the development of antibiotic-resistant strains of organisms. There appear to be three possible mechanisms: (i) strain selection, (ii) adaptation, (iii) mutation. There is evidence of strain selection, for example, with *Staphylococcus pyogenes*. When resistance develops in a bacterial population which was previously wholly sensitive, then there must have been either adaptation or mutation. The question is not yet wholly answered, but there would appear to be strong evidence in favour of mutation.

It is certain that cross-resistance to more than one antibiotic does occur. This is particularly common with aureomycin and terramycin. Chloramphenicol may be involved. Gram-positive cocci and Gram-negative bacilli which develop resistance to aureomycin are very apt to develop resistance to terramycin. This has been shown *in vitro* and does occur *in vivo*.

The problem of the development of antibiotic-resistant strains of organisms has been studied in the Fairfax Institute of Pathology since 1948 by Dr. Phyllis Rountree and myself in association with R. G. H. Barbour, B.Sc. A summary of this work is now given to illustrate the problem generally, and in particular the problem as it affects a large hospital. In 1948 it was evident from observations made in the routine bacteriology laboratory that many strains of *Staphylococcus pyogenes* isolated from patients were resistant to penicillin. Barber (1947*a*, 1947*b*) and Barber and Rozwadowska-Dowzenko (1948) had shown that in a London hospital the incidence of resistant strains had risen from 14% to 38% in a year, and later rose to 59 in 100 cases. It will be seen from Tables I and II that there has been a steady increase in the incidence of penicillin-resistant and streptomycin-resistant strains of *Staphylococcus pyogenes* in various parts of the world.

From October, 1948, to March 31, 1949, we examined 228 strains of *Staphylococcus pyogenes* isolated from 196 patients. The incidence of strains resistant to penicillin and streptomycin, the only two antibiotics in use at that time, is shown in Table III; the incidence of resistant strains was 53% to penicillin and 5% to streptomycin.

From April, 1949, to the end of March, 1950, we examined 603 strains of *Staphylococcus pyogenes* isolated from 513 in-patients and 90 out-patients. The results are shown in Table IV, the incidence of resistant strains among in-patients being 53·4% resistant to penicillin and 14·0% resistant to streptomycin. Although this figure of 53·4% penicillin-resistant strains among in-patients cannot be directly compared with the previous figures given in Table III, which included both in-patients and out-patients, when the two types of patients are combined in the second series the incidence becomes 49%, which is close to that of the first series (53%). The incidence of streptomycin-resistant strains had risen from 5% to 14%.

The monthly incidence of penicillin-resistant and of streptomycin-resistant strains during this period is shown in Figure I. The incidence is expressed as percentages of the total number of strains of *Staphylococcus pyogenes* examined each month. The figure shows clearly the increase month by month in the incidence of strains resistant to streptomycin.

In more recent work, which is at present in the press, we have ascertained the present position with regard to

TABLE II.

Incidence of Streptomycin-Resistant Staphylococcus Pyogenes.

Author.	Place.	Date.	Source of Strains.	Number Examined.	Percentage of Resistant Strains.
Martyn.	Manchester.	1949	0 to 7 day infants:		
			Nose	81	3·7
			Fæces	66	1·5
Barber and Whitehead.	London.	1949	Infections in hospital patients	111	Nil
Rountree and Thomson.	Sydney.	1949	Hospital patients	196	3·5
Rountree, Barbour and Thomson.	Sydney.	1949	Hospital in-patients	513	14
		1950	Hospital out-patients	90	0·9

penicillin-resistant and streptomycin-resistant strains of *Staphylococcus pyogenes*. In addition we have investigated the incidence of strains resistant to aureomycin, chloramphenicol and terramycin. The results are summarized in Figure II. The period covered is the fifteen months from January 1, 1951, to March 31, 1952. The monthly incidence of antibiotic-resistant strains isolated from 1049 patients is shown.

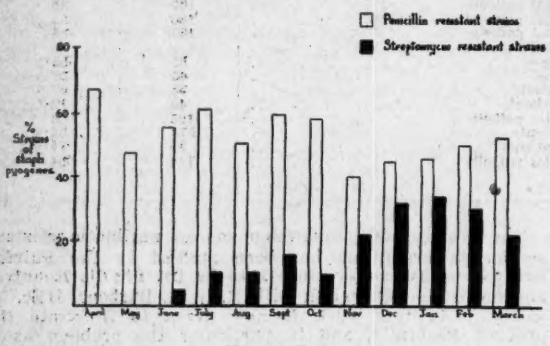

FIGURE I.

Incidence of penicillin-resistant and of streptomycin-penicillin-resistant strains of *Staphylococcus pyogenes* isolated from April, 1949, to March, 1950. (From Rountree, Barbour and Thomson, 1951.)

Penicillin.

Of the in-patient strains, 690 (65·7%) were penicillin-resistant; this, when compared with the figure of 53·4% of 602 strains during the period from April, 1949, to March, 1950, shows an increase of 12·3%. This is statistically significant. There has also been an increase of resistant strains from out-patients, the incidence rising from 24·6% to 36·3%.

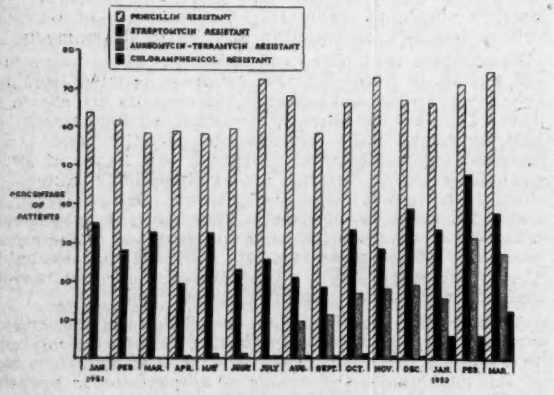

FIGURE II.

Incidence of antibiotic-resistant strains of *Staphylococcus pyogenes* isolated from in-patients.

Streptomycin.

All strains resistant to streptomycin were also resistant to penicillin. The monthly incidence of these strains in in-patients fluctuated from 18·3% to 47·7%, with a mean value of 29·5%, which is approximately the same as that found in the period from December, 1949, to March, 1950.

Aureomycin and Terramycin.

Aureomycin and terramycin are considered together, since it has been found that every strain resistant to one of them has also been resistant to the other. The first strain was isolated in April, 1951. Thereafter there were two, two and one strains in May, June and July respectively. In August eight strains were isolated, and in February, 1952, 21 of 67 strains (31·3%) were resistant. There has been then a steady increase in the incidence of resistant strains.

Chloramphenicol.

From July, 1951, to January, 1952, only 11 strains resistant to chloramphenicol were found. However, in March, 1952, eight of 67 strains (12%) were resistant. It would seem, therefore, that resistant strains are appearing in greater numbers, and it is expected that there will be a rising incidence, as has been seen in the case of the other antibiotics.

TABLE III.[1]

Incidence of Penicillin-Resistant and Streptomycin-Resistant Strains of Staphylococcus Pyogenes from October, 1948, to March 21, 1949.

Antibiotic-Resistance.	Number of Patients.	Number of Strains and Percentage of Total.
Penicillin-sensitive	104	107 (47%)
Penicillin-resistant	92	121 (53%)
Streptomycin-sensitive	189	216 (95%)
Streptomycin-resistant	7	12 (5%)

[1] From Rountree and Thomson (1949).

Nasal Carrier Rates of Antibiotic-Resistant Strains in the Hospital Staff.

In a previous paper (Rountree and Thomson, 1949) it was shown that 64 (32%) of 200 members of the hospital staff were nasal carriers of penicillin-resistant strains of

TABLE IV.[1]

Incidence of Penicillin-Resistant and Streptomycin-Resistant Strains of Staphylococcus Pyogenes from April, 1949, to March 31, 1950.

Antibiotic Resistance.	Number of Patients and Percentage of Total.	
	In-Patients.	Out-Patients.
Penicillin-sensitive	239 (46·6%)	68 (75·4%)
Penicillin-resistant	274 (53·4%)	22 (24·6%)
Streptomycin-sensitive	441 (86·0%)	89 (98·9%)
Streptomycin-resistant	72 (14·0%)	1 (1·1%)

[1] From Rountree, Barbour and Thomson (1951).

Staphylococcus pyogenes. It was later found (Rountree and Barbour, 1951) that nasal carriage of these hospital strains was established in new nursing trainees within a few weeks of their entering the hospital wards, particularly if they were non-carriers on entry. For convenience Figure III is reproduced here to illustrate this point.

TABLE V.

Distribution of Resistant or Sensitive Strains of Staphylococcus Pyogenes among 109 Nasal Carriers.

Antibiotic.	Number of Carriers.	Percentage of Carriers.
Penicillin resistant	88	80·7
Penicillin and streptomycin resistant	51	46·8
Penicillin, streptomycin, aureomycin and terramycin resistant	17	15·6
Penicillin, streptomycin, aureomycin, terramycin and chloramphenicol resistant	3	2·7
Penicillin, streptomycin, aureomycin, terramycin and chloramphenicol sensitive	21	18·4

In February, 1952, the noses of 200 of the nursing and medical staff were swabbed in order to find out what proportion was now carrying antibiotic-resistant strains in relation to penicillin, streptomycin, aureomycin, terramycin and chloramphenicol. There were 109 (54·5%) nasal carriers of *Staphylococcus pyogenes*, which is a rate similar to that found on previous occasions. The distribution of antibiotic resistance among these 109 carriers is shown in Table V.

TABLE VI.

Incidence of Strains of Bacterium Coli Resistant to Streptomycin, to Aureomycin, to Chloramphenicol and to Terramycin from January 1, 1950, to March 31, 1951.

Antibiotic.	January 1, 1950, to June 30, 1950.		July 1, 1950, to September 30, 1950.		October 1, 1950, to December 31, 1950.		January 1, 1951, to March 31, 1951.	
	Number of Strains.	Percentage Resistant.	Number of Strains.	Percentage Resistant.	Number of Strains.	Percentage Resistant.	Number of Strains.	Percentage Resistant.
Streptomycin ..	115	46·9	87	48·3	122	47·6	514	51·8
Aureomycin ..	—	—	65	30·8	112	61·7	514	67·8
Chloramphenicol	—	—	56	19·7	112	33·0	514	41·6
Terramycin ..	—	—	25	24·0	112	35·0	514	57·8

It is interesting to note that only 21 of the people whose noses were swabbed were carrying penicillin-sensitive strains, and it is significant that 10 of these 21 were first-year trainee nurses who had been in the hospital for only a short period.

After the first series of figures for the incidence of antibiotic-resistant strains of *Staphylococcus pyogenes* had been obtained, it was decided to ascertain the incidence of antibiotic-resistant strains of Gram-negative bacilli. The full analysis of this investigation is in the press, and a summary only in relation to *Bacterium coli*, *Proteus vulgaris* and *Pseudomonas pyocyanea* will be given here. The period under review is the fifteen months from January 1, 1950, to March 31, 1951, and the antibiotics are streptomycin, aureomycin, chloramphenicol and terramycin. The results are shown in Tables VI, VII and VIII.

Pseudomonas Pyocyanea.—Of *Pseudomonas pyocyanea*, 214 strains were tested with streptomycin, 129 strains with aureomycin and chloramphenicol, and 121 strains with terramycin. This organism is very resistant to all antibiotics, and the incidence of strains resistant to terramycin has risen from 52·6% to 71·0%.

The Appearance of Other Organisms Which Have Not at Any Time Shown Sensitivity to Any Antibiotic.

The term "superinfection" has been coined to describe fresh complicating infections occurring during antibiotic therapy. This condition is well described in an editorial in a recent number of the *British Medical Journal*. It is known that the use of antibiotics suppresses the general flora of certain areas of the body. This suppression is seen in the mouth when penicillin is being used, and in the gastro-intestinal tract when aureomycin, terramycin or chloramphenicol is being used. This suppression, of course, does not affect those organisms, such as fungi, which are not affected by any antibiotic, nor does it affect those organisms, such as *Pseudomonas pyocyanea*, which are almost completely antibiotic-resistant, or staphylococci and Gram-negative bacilli which have developed resistance. Some of the commoner forms of "superinfection" include infections of the mouth or respiratory passages with *Candida albicans* (monilia), the appearance of *Candida albicans* in superficial and deep skin ulcers or in the female genital tract and the lower part of the bowel, and sometimes the appearance of other fungous infections, such as aspergillosis, in the respiratory system. This condition of "superinfection" may well become a problem of the greatest importance both in hospitals and in general prac-

TABLE VII.

Incidence of Strains of Proteus Vulgaris Resistant to Streptomycin, to Aureomycin, to Chloramphenicol and to Terramycin from January 1, 1950, to March 31, 1951.

Antibiotic.	January 1, 1950, to June 30, 1950.		July 1, 1950, to December 31, 1950.		January 1, 1951, to March 31, 1951.	
	Number of Strains.	Percentage Resistant.	Number of Strains.	Percentage Resistant.	Number of Strains.	Percentage Resistant.
Streptomycin	70	12·9	151	25·3	160	32·5
Aureomycin	—	—	77	92·2	160	87·5
Chloramphenicol	—	—	77	36·3	160	36·9
Terramycin	—	—	72	84·8	160	86·9

Bacterium Coli.—The strains of *Bacterium coli* tested with streptomycin numbered 838; 691 strains were tested with aureomycin, 682 strains with chloramphenicol and 651 strains with terramycin. The percentage of strains resistant to streptomycin has remained fairly constant at 46·9 to 51·8. The percentage of strains resistant to aureomycin has risen from 30·8 to 67·8, which is statistically significant. A similar trend may be occurring with chloramphenicol, with which the percentage of resistant strains has risen from 19·7 to 41·6, and with terramycin, with which the rise has been from 24·0 to 37·8.

Proteus Vulgaris.—Of *Proteus vulgaris*, 331 strains were tested with streptomycin, 237 strains with aureomycin and chloramphenicol, and 232 strains with terramycin. There has been an increase in streptomycin-resistant strains from 12·9% to 32·5%.

TABLE VIII.

Incidence of Strains of Pseudomonas Pyocyanea Resistant to Streptomycin, to Aureomycin, to Chloramphenicol and to Terramycin from January 1, 1950, to March 31 1951.

Antibiotic.	January 1, 1950, to June 30, 1950.		July 1, 1950, to December 31, 1950.		January 1, 1951, to March 31, 1951.	
	Number of Strains.	Percentage Resistant.	Number of Strains.	Percentage Resistant.	Number of Strains.	Percentage Resistant.
Streptomycin	68	50·0	63	58·7	83	53·0
Aureomycin	—	—	46	93·5	83	92·8
Chloramphenicol	—	—	46	82·6	83	83·1
Terramycin	—	—	38	52·6	83	71·0

tice. It may well prove to be a fatal infection in some cases.

Discussion.

It will be seen from the facts given above that there has been in this hospital a rising incidence of antibiotic-resistant strains of *Staphylococcus pyogenes* and of the Gram-negative bacilli since the introduction of antibiotic therapy. It is probable that the facts which present themselves in this hospital indicate fairly accurately the state of affairs in the majority of large hospitals. It must be stressed that the problem would appear to be one of institutions, and that the incidence of antibiotic-resistant strains of organisms occurring in general practice is not yet of serious consequence; but it should be noted that there has been an increase in antibiotic-resistant strains of *Staphylococcus pyogenes* in the out-patient department.

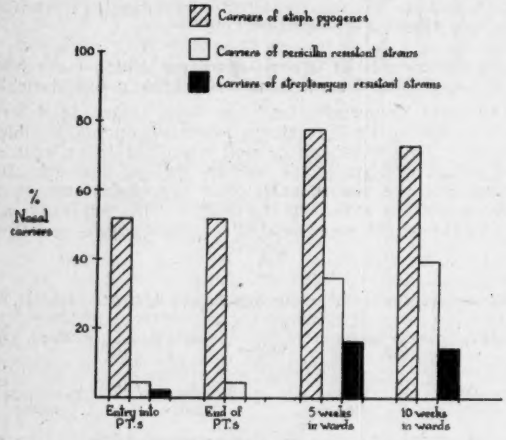

FIGURE III.

Nasal carrier rates of *Staphylococcus pyogenes* and of penicillin-resistant and streptomycin-resistant strains of *Staphylococcus pyogenes* in 104 trainee nurses swabbed on four occasions in sixteen weeks. P.T.S. = preliminary training school. (Adapted from Rountree and Barbour, 1951.)

To illustrate the practical application of all this, it is interesting to note the following facts, which it is considered are important. In the period from July, 1950, to June, 1951, seven strains of *Staphylococcus pyogenes* which were completely resistant to penicillin, streptomycin, aureomycin, terramycin and chloramphenicol were isolated. In the period from July, 1951, to March, 1952, 44 such strains were isolated. In these same two periods the figures for *Bacterium coli* were 75 and 88 antibiotic-resistant strains, and for *Proteus vulgaris* 16 and 21 antibiotic-resistant strains, respectively. In the period of three months from January 1, 1952, to March 31, 1952, the following figures were obtained for strains sensitive to chloramphenicol only: for *Staphylococcus pyogenes*, 60 (14%) of 426 strains; for *Bacterium coli*, 31 (6%) of 514 strains; for *Proteus vulgaris*, 78 (25%) of 303 strains; for *Pseudomonas pyocyanea*, 15 (21%) of 71 strains. These figures are important when one considers the fact that the incidence of strains resistant to chloramphenicol has begun to increase.

There have also been recently three cases of cross-infection—two of pneumonia and one of septicæmia—due to *Staphylococcus pyogenes* resistant to all antibiotics. These three patients died.

Conclusion.

In conclusion it is suggested that the following facts merit consideration.

1. Adequate bacteriological examination and adequate antibiotic sensitivity tests are essential whenever practicable.

2. Resident medical officers and medical students should be told that there was a "preantibiotic" era, in which patients did recover from infective processes without the use of antibiotics.

3. Antibiotics should not be used as universal antipyretics.

4. The importance of sound clinical judgement must never be forgotten, and the temptation to give antibiotics "in case" or to appease the relatives must be overcome.

5. Antibiotics should not be necessary in the "clean" surgical case if it is remembered that antibiotics do not replace asepsis.

Acknowledgements.

It is desired to acknowledge the very valuable technical assistance of Mr. George Barr and Miss Vera Sife.

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OBSERVATIONS ON THE UTILITY OF HÆMAGGLUTINATION AND HÆMOLYTIC TESTS IN PULMONARY TUBERCULOSIS.

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SINCE the end of the last century it has been the aim of a number of investigators to design a serological test capable of assisting the clinician in the diagnosis and treatment of tuberculosis. Agglutination, complement fixation and precipitation methods were tried; a critical survey of these was given by Topley and Wilson (1946). In 1945, Muether and MacDonald described a test in which the agglutinating power of the sera was titrated against suspensions of *Serratia marcescens* coated with tuberculin.

None of these methods has become popular, presumably because the results were difficult to interpret and did not help the physician materially in assessing clinical state and prognosis and in deciding on management.

The description by Middlebrook and Dubos (1948) of a new serological method therefore aroused considerable interest. These workers coated washed sheep erythrocytes with a phenol-insoluble and water-soluble fraction of tubercle bacilli and found that the cells thus sensitized were agglutinable by specific immune serum and by serum of patients suffering from tuberculosis. It may be noted that agglutination by specific antisera of erythrocytes sensitized with extracts obtained from a number of different bacterial species was first reported by Keogh, North and Warburton (1947), and that their observations formed the basis of a diagnostic test for *Hæmophilus influenzæ* (type b) menin-

gitis (Warburton, Keogh and Williams, 1949). After the report of Middlebrook and Dubos several papers appeared in which results of clinical applications of their serological test for tuberculosis were given. Some of the authors closely followed the methods of Middlebrook and Dubos (1948) (Gernez-Rieux and Tacquet, 1949 and 1950; Sievers, Ulstrup and Winblad, 1950); others, however, replaced the bacterial extract, used for sensitizing the erythrocytes, with tuberculin (Gernex-Rieux and Tacquet, 1950; Rothbard, Dooneief and Hite, 1950; Scott and Smith, 1950; Smith and Scott, 1950; Sohier, Juillard and Trimberger, 1950). The hæmagglutination method was reviewed by Middlebrook (1950*a*) and in an editorial (*The Lancet*, 1950).

A modification of the hæmagglutination technique was reported by Fisher and Keogh (1950), who found that hæmolysis took place on the addition of complement to suspensions of sensitized cells in specific immune sera. The phenomenon was independently observed by Middlebrook (1950*b*) and was also encountered by Muniz (1950) in the course of work on trypanosomal antigens.

The purpose of this paper is to report the results obtained on testing a number of sera, from tuberculous and non-tuberculous subjects, by the hæmolytic technique, and to compare the findings with those of other workers who used hæmagglutination methods.

Technique of Tests.

As the method has been described in detail elsewhere (Fisher, 1950, 1951), the present account will be brief. Heat-killed, dried organisms of the virulent PN strain of *Mycobacterium tuberculosis*, human type, were thoroughly extracted with phenol (90%). The insoluble residue was washed with acetone and dried. Aliquots were extracted with buffered methanol saline (Middlebrook and Dubos, 1948) and filtered through paper. Washed sheep erythrocytes were sensitized by being suspended in the filtrate. The cells were then allowed to form a sediment in the centrifuge, repeatedly washed, and finally resuspended in saline.

Specimens of blood were obtained by venepuncture and allowed to clot. The serum was separated and inactivated at 56° C. for thirty minutes. Prior to being tested, all sera were absorbed with washed sheep cells in order to remove natural antisheep erythrocyte hæmagglutinins and hæmolysins. Serial dilutions of the serum were then prepared, mixed with the sensitized cells, and placed in the water bath at 37° C. for not less than ten minutes.

Complement, in the form of fresh guinea-pig serum, diluted with saline, and absorbed with washed sheep erythrocytes, was then added to all tubes; the latter were returned to the water bath and removed for reading of results when the hæmolysis in the titration of a reference rabbit serum, included with every batch of tests on unknown sera as a positive control, had proceeded to the accustomed serum dilution. The following "negative" controls were set up; unsensitized cells in the test sera and complement; unsensitized and sensitized cells in complement.

When it was desired to record hæmagglutination titres, the cells were allowed to settle prior to the addition of the complement. The degree of hæmagglutination was read according to sedimentation pattern.

Titres are expressed in terms of the reciprocal of the highest serum dilution giving complete hæmolysis or hæmagglutination.

Results.

Titres Obtained on Sera of Non-tuberculous Subjects.

One group of sera were obtained from trainee nurses who had been found free from tuberculosis by X-ray examination of the chest and by general physical examination, and who failed to react to the Mantoux test with 0·1 millilitre of 1:1000 old tuberculin; they were not tested with tuberculin of higher concentration, to which some of them might have reacted. The other group of sera was taken from in-patients of medical and surgical wards in whom tuberculosis could not be detected by X-ray examination of the chest and by general physical examination, and a few (five) from medical students who, with the exception of one, had reacted to the Mantoux test and in whom X-ray examination of the chest did not show tuberculosis.

The results are shown in Table I. Of the 20 sera from the nurses, nine (45%) contained antibody in a titre of not less than 5; in one case the titre reached 80. In the other group, 12 sera out of 82 (14·6%) gave a titre of not less than 5; no antibody could be demonstrated in any of the specimens taken from the medical students. The titre of 80 was found in the serum of a woman, aged fifty-nine years, suffering from gross rheumatic mitral and aortic heart disease. One of the sera giving the titre of 40 was obtained from a boy, aged sixteen years, with gross sinusitis and nasal obstruction, and the other from a woman, aged sixty-nine years, suffering from anxiety state and sinusitis.

The incidence of reacting sera in the trainee nurses was higher than in the medical students or patients, and the difference is statistically significant ($P = 0·004$). In the two groups combined, the overall incidence of sera reacting in the test to a titre of not less than 5 was 21 specimens out of 102 (20·6%).

Titres Obtained on Sera of Patients Suffering from Pulmonary Tuberculosis.

Single specimens were examined from 87 patients suffering from pulmonary tuberculosis. Table I gives the distribution of the titres. Since the initial serum dilution in these tests was 1:5, the lowest demonstrable titre was 5. In thirty of the sera there was insufficient antibody to give a positive result in this titre. Five sera gave a titre of 5, ten sera a titre of 10, fifteen a titre of 20, eight a titre of 40, fifteen a titre of 80, two a titre of 160 and one each titres of 320 and 640. If serum giving a titre of not less than 5 is taken as one giving a positive result, 57 sera out of 87 (65·5%) thus gave positive results.

In order to classify the cases, the four-digit code of the World Health Organization was used. This code has never been published; it was submitted to one of the meetings of the Expert Committee on Tuberculosis in 1949 in the form of a "working paper" (see World Health Organization, 1950), and circulated to a number of governments and

TABLE I.

Sera of Non-Tuberculous and of Tuberculous Subjects: Titres Obtained by the Hæmolytic Technique.

Group.	Number of Sera Giving Titre of									Total.
	<5.	5.	10.	20.	40.	80.	160.	320	640.	
Trainee nurses	11	1	3	2	2	1	—	—	—	20
Medical students and patients free from tuberculosis	70	5	4	—	2	1	—	—	—	82
Total	81	6	7	2	4	2	—	—	—	102
Patients suffering from pulmonary tuberculosis	30	5	10	15	8	15	2	1	1	87

TABLE II.

Titres of Individual Sera and Clinical Classification of Patients by the Four Digit Code (World Health Organization).

Serum.		Code.[1]				Serum.		Code.				Serum.		Code.			
Number.	Titre.	T.	C.	L.	P.	Number.	Titre.	T.	C.	L.	P.	Number.	Titre.	T.	C.	L.	P.
64	<5	1	0	0	0	110	5	9	0	5	0	87	40	1	0	8	1
74	<5	1	0	0	0	109	5	9	0	8	5	94	40	0	2	8	4
76	<5	1	0	0	0	101	5	9	3	4	1	40	40	0	3	7	2
45	<5	1	0	1	0	119	5	9	9	9	9	37	40	0	3	8	5
65	<5	1	0	1	0	108	5	9	Px	Px	1	52	40	0	3	8	9
98	<5	1	0	1	0	18	10	1	0	5	2	44	40	0	4	7	2
77	<5	1	0	2	0	97	10	1	0	PE	0	21	40	0	4	8	5
120	<5	1	0	2	0	22	10	1	1	1	4	105	40	0	9	9	9
50	<5	1	0	PE[2]	3	51	10	1	Px	Px	0	24	80	1	0	2	0
123	<5	1	1	2	0	122	10	4	0	5	0	40	80	6	1	5	0
118	<5	1	0	8	4	43	10	7	0	5	2	42	80	0	0	5	1
82	<5	1	0	8	9	98	10	0	1	7	2	57	80	0	0	5	6
181	<5	4	0	2	0	103	10	0	5	8	4	16	80	0	1	2	1
84	<5	4	Th[2]	Th	1	107	10	0	7	8	4	19	80	0	1	2	2
61	<5	5	0	2	0	54	10	0	0	0	0	92	80	0	2	6	2
114	<5	6	0	0	1	58	20	1	0	0	0	88	80	0	2	7	9
55	<5	6	1	2	0	25	20	1	0	1	2	67	80	0	3	8	2
60	<5	6	1	7	2	89	20	1	0	6	0	53	80	0	6	7	3
73	<5	9	0	3	1	129	20	1	0	Px	0	14	80	0	9	9	9
124	<5	9	1	2	1	33	20	1	Th	Th	4	20	80	0	9	9	9
99	<5	9	1	Px[2]	4	85	20	4	Th	Th	5	56	80	0	9	9	9
17	<5	9	3	2	1	62	20	0	0	7	1	15	80	0	Px	7	5
104	<5	9	3	8	4	89	20	0	0	8	3	100	80	0	Px	Px	4
90	<5	9	3	9	9	113	20	0	1	8	5	79	160	1	6	8	4
86	<5	9	3	Th	1	13	20	0	3	8	0	102	160	0	0	8	4
12	<5	9	4	3	3	130	20	0	4	8	1	59	320	6	1	6	1
80	<5	9	4	7	2	111	20	0	6	9	4	112	640	0	1	5	1
66	<5	9	7	8	1	38	20	0	8	8	4						
91	<5	9	8	8	4	75	20	0	0	0	0						
63	<5	9	0	9	9	23	20	0	Px	Px	5						

[1] Code T refers to tubercle bacilli; Code C, to cavitation; Code L, to lesions; Code P, to principal symptoms. In all digits, higher figures indicate greater severity.

[2] PE, pleural effusion; Th, thoracoplasty; Px, pneumothorax. These conditions prevented assessment of the values of digits C and L. The use of the notation "PE" is a deviation from the recommendations issued for the use of the code.

unofficial bodies, comments being invited. It is similar to the less detailed classification of Hilleboe and Holm (1946).

The first digit (T) of the code refers to bacteriological findings; codes 1 to 4 indicate inability to demonstrate the tubercle bacillus; code 5 indicates the lack of specimen to be examined; and codes 6 to 9 indicate positive findings. The second digit (C) refers to cavitation: if no cavities are demonstrable by X rays, code 0 is used; suspected cavitation is denoted by codes 1 and 2, and definite cavitation by codes 3 to 9, according to the extent. The third digit (L) classifies the extent of the lesions; code 0 is used when pleural effusion is present; the degree of involvement, measured according to the number of intercostal spaces in which lesions can be seen in the X-ray film, is expressed by codes 1 to 9. The "principal symptoms"—temperature elevation, weight loss and fatigue—graded in codes 0 to 9, constitute the fourth digit (P). In digits C and L the code numbers are replaced by the signs "Px" and "Th", if the identification of the cavity or lesion is prevented by pneumothorax or thoracoplasty, respectively.

Thus the higher the digit value, the greater the ease in demonstrating the specific organism (T), the more severe the cavitation (C), the more extensive the disease (L), and the more pronounced the symptoms and physical signs (P).

The titres of the individual sera and the corresponding digit values are set out in Table II, in order of increasing serum titres. To detect any correlation between digit values and serological titres, the data in Table II were analysed as follows. The cases were divided into two groups, those with serum titres of 10 or less in one, and those with titres of 20 or more in the other. For each of the four digits these two groups were then subdivided by setting out the number of cases occurring for each digit value. For each horizontal row the "average digit value" was then calculated, by dividing the sum of all the digit values in the row by the number of observations. The "average digit values" for the four digits, the value for the lower titre group being put first, are as follows: T, 5·7 and 7·2; C, 2·0 and 3·0; L, 4·5 and 6·7; and P, 2·3 and 3·6 (Table III).

The "average digit values", by themselves meaningless, served to indicate that higher titres were associated with higher digit values for each of the four digits of the code.

TABLE III.

Classification of Cases of Pulmonary Tuberculosis According to Serum Titres and Values of the Digits.
(Derived from Table II.)

Serum Titre.	Digit.	Number of Cases Assessed at Digit Value of										Total Number of Cases.	"Average Digit Value."
		0[1]	1	2	3	4	5	6	7	8	9		
10 or less ..	T. (Tubercle bacilli.)	—	16	—	—	3	1	3	1	—	21	45	5·7
20 or more ..		—	8	—	—	1	—	2	—	—	31	42	7·2
10 or less ..	C. (Cavitation.)	21	7	—	5	2	1	—	2	1	3	42	2·0
20 or more ..		11	6	1	7	3	—	3	—	1	5	37	3·0
10 or less ..	L. (Lesions.)	4	4	8	2	1	4	—	3	8	4	38	4·5
20 or more ..		1	1	3	—	—	4	2	6	14	6	37	6·7
10 or less ..	P. (Principal symptoms.)	16	9	5	2	7	1	—	—	—	5	45	2·3
20 or more ..		6	7	6	2	7	7	—	—	—	7	42	3·6

[1] Value 0 is not used for digit T.

In order to test the significance of these trends, the section for each digit in Table III was divided by a vertical line so as to give two groups containing approximately the same number of observations. Each of these two groups was then divided into two further groups according to titres as before. For each digit, therefore, the number of observations was divided into four groups, according to titre and digit value. Examination of these distributions showed that the association of the higher titres with the higher digit values was statistically significant for each digit of the code—that is, higher titres were associated with more severe clinical, bacteriological and radiological findings (Table IV).

TABLE IV.

Significance of Correlation between Severity, as Expressed by Digit Value, and Serum Titre.

(Derived from Table III.)

Code Digit.	Serum Titre.	Number of Cases in		Significance.
		Lower Value Digit Group.	Higher Value Digit Group.	
T (Tubercle bacilli)	10 or less. 20 or more.	24 } D.G.[1] 11 } 1 to 8	21 } D.G. 31 } 9	$P=0{\cdot}006$
C (Cavitation)	10 or less. 20 or more.	28 } D.G. 17 } 0 and 1	14 } D.G. 20 } 2 to 9	$P=0{\cdot}03$
L (Lesions)	10 or less. 20 or more.	23 } D.G. 11 } 0 to 6	15 } D.G. 26 } 7 to 9	$P=0{\cdot}005$
P (Principal symptoms)	10 or less. 20 or more.	25 } D.G. 13 } 0 and 1	20 } D.G. 29 } 2 to 9	$P=0{\cdot}01$

[1] D.G. = digit grouping.

Since, owing to the nature of the disease, the manifestations, as expressed by the digits, can be expected to show generally parallel trends, it is not surprising that the values in each digit are correlated to the serological titre. This relationship also holds for the cases in which positive bacteriological findings were obtained; of nine sera from patients with L digit values of four or less, only two had titres in excess of 10; of 44 with corresponding L digit values of five or over, 29 had titres of 20 or more.

In spite of this general correlation, however, the serological titre failed to correspond to the assessment given by the code in a considerable number of individual cases (Table II). In Cases 19 and 16, for instance, the patients with serum titres of 80 had lesions of minimal or slight extent and of low activity. On the other hand, titres of patients giving the digit values 9999—that is, suffering from extremely severe and extensive disease—covered a range from <5 to 80. Of these patients, two (Case 63, titre <5, and Case 75, titre 20) died within a short time; three patients (Case 14, titre 80, Case 54, titre 10, and Case 105, titre 40) were alive, though very ill, after sixteen months; one patient (Case 20, titre 80) showed symptomatic improvement after twenty months; and one patient (Case 119, titre 5) was considerably, and entirely unexpectedly, improved after sixteen months.

Correlation Between the Results of Hæmagglutination and Hæmolytic Tests on Human Sera.

Middlebrook (1950*b*) examined seven "representative" sera, by both hæmagglutination and hæmolytic methods, against cells sensitized with Lederle tuberculin, and found that in some sera the hæmagglutination titres were higher, and in others the hæmolytic titres. He concluded that results obtained by the two methods were not correlated. Since our routine tests were carried out by the hæmolytic technique, and with the use of bacterial extract as the erythrocyte-sensitizing agent, the question arose whether Middlebrook's conclusions could be supported by titrations on our sera. With regard to the effect of using different sensitizing agents, cells coated with a sample of a special concentrated tuberculin (four times the strength of the international standard), kindly supplied to us by the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York, United States of America, were tested against a number of sera, in parallel with cells sensitized with our extract, in hæmagglutination and hæmolytic titrations. Titres obtained against the two lots of cells showed close correlation; details of these tests will not be given here. Correlation between titres obtained in hæmagglutination and hæmolytic tests on human sera was examined as follows.

A number of specimens were selected, mostly from the groups of sera of non-tuberculous and tuberculous subjects referred to above, and examined in hæmagglutination and hæmolytic tests, erythrocytes sensitized with our bacterial extract being used.

Of the 89 sera of non-tuberculous subjects examined, 70 failed to react in both tests. One specimen of serum showed hæmagglutination in the lowest detectable titre, but no reaction in the hæmolytic test. Sixteen sera, giving a negative response in the hæmagglutination test, gave hæmolytic titres ranging from 5 to 80. Two sera reacted in both tests; the hæmagglutination titre of each was 5, and the hæmolytic titre of one was 10 and of the other 80 (Table V).

TABLE V.

Relationship Between Hæmagglutinating and Hæmolytic Serum Titres.

Group.	Hæmagglutinating Titre.	Hæmolytic Titre.	Number of Observations.
Persons free from tuberculosis.	<5	<5	70
	<5	5	5
	<5	10	4
	<5	20	1
	<5	40	5
	<5	80	1
	5	<5	1
	5	10	1
	5	80	1
Total	—	—	89
Patients suffering from pulmonary tuberculosis.	<5	<5	2
	<5	5	1
	<5	10	1
	<5	20	2
	<5	40	1
	5	10	2
	10	40	1
	10	80	2
	10	320	1
	20	40	1
	20	640	1
	40	320	2
	40	640	1
Total	—	—	18

Eighteen sera were examined from the tuberculous group. Of these, two gave negative results in both tests. In five the hæmolytic test only produced a positive result, the titres ranging from 5 to 40. Both tests gave positive results on eleven sera; the hæmagglutinating titres of these varied between 5 and 40, and the hæmolytic titres between 10 and 640 (Table V).

There were thus 35 sera altogether which gave positive results to one or both tests. In all but one the hæmolytic titre exceeded the hæmagglutinating titre. The ratio of hæmolytic titre to hæmagglutinating titre, in the specimens giving definite readings in both tests, varied from 2:1 to 32:1, the geometric mean being between 4:1 and 8:1.

While this variation of the ratios of the titres obtained in the two tests was in accordance with the findings of Middlebrook (1950*b*), in his results the hæmolytic titres were relatively lower. This may have been due to minor differences in the details of technique and in the reading of results; the amount of complement used is a decisive factor in titres obtained in hæmolytic tests (Fisher, 1950).

TABLE VI.

Results Obtained by Different Authors in Reactions of Sera Against Erythrocytes Sensitized with Tuberculin or Extracts of Tubercle Bacilli.[1]

Authors.	Technique.	Erythrocyte Sensitizing Agent.	Persons Free from Tuberculosis.			Persons Suffering from Tuberculosis.		
			Number Reacting.	Number Not Reacting.	Percentage Reacting.	Number Reacting.	Number Not Reacting.	Percentage Not Reacting.
Gernez-Rieux and Tacquet (1949)	Hæmagglutination.	Bacterial extract.	13	30	30	83	12	13
Gernez-Rieux and Tacquet (1950)	Hæmagglutination.	Bacterial extract.	1	20	4·8	34	8	19
Sievers *et alii* (1950)	Hæmagglutination.	Bacterial extract.	18	84	18	N.F.S.[2]	N.F.S.	N.F.S.
Gernez-Rieux and Tacquet (1950)	Hæmagglutination.	Tuberculin.	4	17	19	35	7	17
Rothbard *et alii* (1950)	Hæmagglutination.	Tuberculin.	13	203	6·0	147	13	8·1
Scott and Smith (1950)	Hæmagglutination.	Tuberculin.	0	15	0	38	12	24
Smith and Scott (1950)	Hæmagglutination.	Tuberculin.	57	136	29	89	21	19
Sohier *et alii* (1950)	Hæmagglutination.	Tuberculin.	0	15	0	20	10	33
Totals			106	520	16·9	446	83	15·7
Present investigation	Hæmolysis.	Bacterial extract.	21	81	20	57	30	34

[1] In the compilation of this table, results in Mantoux tests were not taken into account. Subjects who had received BCG vaccination were not included, nor were any in whom the presence or absence of tuberculosis did not appear reasonably certain.

[2] "N.F.S.", no figures suitable for inclusion in this table available.

It is thought, from the results shown in Table V, that if parallel tests with the two techniques were carried out on larger series, and the "diagnostic titres"—that is, the titres above which the reactions are considered positive—were carefully established for both methods, good correlation would be present between the results of the two tests.

Discussion.

Table VI shows a summary of available literature on results obtained by the use of the hæmagglutination test in tuberculosis. Of 626 sera from healthy persons or patients suffering from diseases other than tuberculosis, 106 (16·9%) gave positive results; the incidence in the different groups varied from 0 to 30%. In our series, by the use of the hæmolytic technique, 21 sera out of 102 (20·6%) reacted; nine of the reacting sera, however, came from a group of 20 trainee nurses (45%) and the other 12 from 82 non-tuberculous patients or healthy medical students (14·6%). This unexplained difference between the two groups of our series indicates that factors other than tuberculous infection may have important bearings on the result of the test. Variations in the incidence of sera reacting to the hæmagglutination test, in different groups of non-tuberculous subjects, were present in the series of Smith and Scott (1950).

Of 529 sera of tuberculous patients, 83 (15·7%) were reported to have failed to give positive results to hæmagglutination tests; the incidence of failure varied from 8·1% to 33%. In our tuberculous group, 30 specimens out of 87 (34%) gave no reaction. The percentage of failures to obtain positive results to serological tests in selected groups of tuberculous individuals can be expected to be influenced by the average severity of the cases chosen for investigation, since the latter has been found to be correlated to the titre.

In hæmagglutination tests on sera of non-tuberculous subjects, 32 positive results were reported from 166 specimens (19·3%) against cells sensitized with bacterial extract, and 74 out of 460 (11·5%) against cells coated with tuberculin. This would suggest that coating of the cells with tuberculin resulted in a slightly more specific reagent; however, the groups in the series of different authors may not have been strictly comparable. On the sera of tuberculous patients the percentages of negative results obtained against cells sensitized with bacterial extract or tuberculin did not differ quite so much (14·6% and 16·1%, respectively).

All our tests were performed by the hæmolytic method, which thus appeared to give "false positive" and "false negative" results with the same order of incidence as the figures reported in the literature and derived from hæmagglutination tests.

The correspondence between the results of the hæmagglutination and the hæmolytic techniques may not be complete. However, this conclusion has little practical significance, since a test failing to detect up to 34% of cases of pulmonary tuberculosis and yielding positive results in up to 30% of subjects free from tuberculosis would appear to have only a very limited application in the clinical field.

In the series of Smith and Scott (1950) the failure of the test to detect tuberculosis was confined to patients in the terminal stages of the disease. Negative results obtained on sera from patients in all stages of the illness were reported by Rothbard *et alii* (1950), and were also present among our cases.

The occurrence of positive reactions in sera of subjects free from tuberculosis may be wholly or partly due to the presence of antibodies against certain antigenic components distributed over a wide range of mycobacteria (or even other bacterial species), capable of passing into bacterial extracts or tuberculin, and adsorbable to erythrocytes. Evidence of cross-reactions between erythrocyte-adsorbable fractions of different mycobacteria has already been given in detail (Fisher, 1951). Levine (1951) independently reported agglutination of erythrocytes sensitized with tuberculin, by the sera of patients suffering from leprosy.

In the tuberculous group the serological titre was correlated to the severity of the bacteriological, radiological and clinical findings, as expressed by the World Health Organization classification. However, the correlation was not close enough to allow deductions to be drawn about the clinical state of individual patients from the results of the serological tests.

It is possible, though we have no evidence to support this, that serial tests may help in following changes in the activity of the disease, particularly in patients suffering from tuberculosis of organs less readily accessible to diagnostic weapons than the lung.

Sievers *et alii* (1950) noted that the results of the hæmagglutination test and the Mantoux test did not always correspond. Similar results were obtained in our series, the sera being tested by the hæmolytic method. North and Jamieson (1950) reported that of 24 lepers examined in an area of New Guinea where there was practically no tuberculosis, 23 failed to react to the Mantoux test. The sera of a number of lepers have been found to react to the serological test (Fisher, 1951, and unpublished results); some of these patients had been tested for sensitivity to tuberculin and failed to react.

The reaction may prove useful in the management of mycobacterial infections other than tuberculosis — for example, leprosy (Levine, 1951). In an investigation on the use of the test for the detection of mycobacterial infections in cattle, Fisher and Gregory (1951) concluded that the reaction might have an important application in the diagnosis of Johne's disease, a condition in which sensitivity to mammalian tuberculin is usually either weak or absent.

Conclusions.

Reactions between human sera and sheep erythrocytes coated with fractions of tubercle bacilli were not sufficiently specific or sensitive to make the test a helpful one in the diagnosis of tuberculosis, irrespective of whether the hæmagglutination or the hæmolytic method was used. Correlation between clinical state and serological titre in tuberculous subjects, although present, was not close; thus little reliance could be placed on serological titre as a means of the clinical assessment.

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THE TREATMENT OF LEAD POISONING BY THE INTRAVENOUS ADMINISTRATION OF SODIUM THIOSULPHATE.

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AMONG the various agents which have been used or recommended in the treatment of lead poisoning, sodium thiosulphate appears to have suffered from undeserved neglect.

Among the earliest investigators to use sodium thiosulphate intravenously in metallic poisonings were Dennie and McBride (1923, 1924), who in 1920 began the treatment of poisoning by various metallic compounds by this means. Among poisonings successfully treated were those due to arsenic, mercury, bismuth and lead. Their use of sodium thiosulphate was suggested by the work of Ravaut (1920), who treated arsphenamine dermatitis with this agent. Ockerblad (1923) successfully treated with sodium thiosulphate given intravenously a patient suffering from acute lead poisoning, who was passing red cells, albumin and casts in the urine. Dennie and McBride (1924) quote the treatment of a similar patient by R. Mayer, three patients by L. Milne, and three patients by C. Nelson, with excellent results.

In the subsequent period between the appearance of the work referred to above and the work of Pincus (1936), several papers appeared on the use of sodium thiosulphate in the treatment of metallic poisoning due to arsenic, bismuth and mercury compounds.

Semon (1924) reported its successful use in two cases of mercury stomatitis, in one of bismuth stomatitis, in one of bismuth salivation, in one of arsenical jaundice, and in one of acute dermatitis arising after two intravenous injections of sulpharsenol. In the last-mentioned case the pruritus had subsided the day after one dose of 0·5 gramme. In the former cases the dose was 0·45 to 0·6 gramme in 5·0 millilitres of water on alternate days. Three to four doses were sufficient. Semon stated that it was of value also when taken orally in a case of mercurial stomatitis and eruptions, and also as a local antidote to the effects of arsenical injections outside a vein.

Halliday and Sutherland (1925) describe a case of very severe arsenical poisoning in which the patient at one stage was moribund. The patient was treated at first with 30 grains of the stock salt given orally every four hours while the preparation of the pure salt was being awaited. There were no toxic effects from the thiosulphate, but no improvement in the patient's condition, which was deteriorating; after three days the intravenous injections were commenced, the dose being 0·45 gramme daily for ten days and then 0·45 gramme on alternate days for seven days. After the first injection the downward trend was arrested and the patient eventually made a complete recovery.

Aub, Fairhall, Minot and Reznikoff (1926) referred to the earlier work on the treatment of lead poisoning with this agent and stated that the method was worthy of further study.

In spite of this early success the method apparently failed to secure general acceptance.

As late as 1944, Cantarow and Trumper (1944) stated that whereas some beneficial effect was observed in clinical lead poisoning by a few investigators (McBride and Dennie, 1923, 1924; Hegler, 1933), the majority of reports in clinical and experimental plumbism indicated that this agent was of little or no value in this regard (Curtis and Young, 1928; Linguerri, 1933).

Curtis and Young (1928), however, treated their lead-poisoned animals with thiosulphate given orally. They found that sodium thiosulphate given by mouth in doses of 0·05 gramme per kilogram of body weight to guinea-pigs, rabbits and rats previously poisoned by lead did not appreciably affect the excretion of lead. Since their treatment was oral, their results cannot be adduced as evidence against the value of this agent when used intravenously.

Early in 1933 Pincus (1936) commenced to use the method at Mount Isa, where in the period from 1931 to 1936 there were about 300 cases of compensable lead poisoning and many others of lesser degree of severity. Although he was not the only medical practitioner treating these cases, his experience firstly of the then recognized methods of treatment and subsequently of the thiosulphate method was very extensive. He soon came to prefer this method to any other. At this time nothing was definitely known as to the mode of action of the thiosulphate. His experience showed that after thorough treatment with thiosulphate recurrence of symptoms without further exposure was very rare, whereas it was common after calcium therapy.

Further, at Mount Isa it was frequently observed that the blue line (Burton's line) rapidly disappeared under thiosulphate treatment, which indicated that lead sulphide was probably being dissolved, and either eliminated or deposited elsewhere.

Dennie (1924) stated that Meyers had proved beyond doubt that sodium thiosulphate increased the elimination of metals from the body in cases of metallic poisoning, but no figures were given by him.

Subsequent to the appearance of the note by Pincus (1936) several papers on the effect of sodium thiosulphate in experimental lead poisoning in animals and in clinical lead poisoning in humans appeared.

Schmitt and Lossie (1938) found that the intravenous administration of "S-hydril" (that is, stabilized sodium thiosulphate) in one case of clinical lead poisoning resulted in a sudden clinical improvement. The blood lead content was significantly decreased after eight days and returned to normal after fourteen days.

Schmitt and Lossie (1939) stated that sodium thiosulphate administration relieved clinical symptoms, lowered blood lead content and eliminated lead from depots.

In a series of papers on experimental work with rabbits, guinea-pigs and fish, Binet, Pérel and Glotz (1939), Binet and Pérel (1939), Binet, Chauchard and Pérel (1940) showed that the intravenous injection of 0·2 gramme of lead acetate into adult rabbits caused coproporphyrinuria within forty-eight hours, which persisted for weeks if not treated, but disappeared in two days if one gramme of sodium thiosulphate was injected daily; that sodium thiosulphate counteracted the toxic action of lead salts in experimental lead poisoning paralysis and prevented paralysis from occurring; and that this salt, suitably administered, protected fish and guinea-pigs from lethal doses of lead subacetate.

Sabatini, Molfino and Mazzatini (1937) showed that intramuscular injections of various preparations of sulphur were followed by diuresis and increased urinary lead output. Patients showed a rapid improvement in general condition and a progressive diminution in the clinical symptoms of lead poisoning. Their paper is not available in Australia, and the abstract does not specify the method of administration.

The Present Investigation.

In view of the fact that the value of this agent is apparently still not widely recognized and that the search for other satisfactory agents still goes on, as witness the somewhat unfavourable results of the use of BAL (British anti-Lewisite—2,4-dimercaptopropanol) (Vigliani and Zurlo, 1951), it has seemed worth while to describe in more detail than appears in the note of Pincus (1936) some of the results obtained with this agent at Mount Isa and subsequently in Melbourne.

Most of the work discussed in this paper was done in 1934, 1935 and 1936. Experience in the subsequent years has confirmed the value of the method. It is proposed to deal in a separate paper with the effects of the intravenous use of sodium thiosulphate on urinary lead concentration at Mount Isa, and with recent work in Melbourne on the effects on blood lead concentration and on lead excretion in urine and fæces.

In about the year 1935 Mount Isa was the largest single lead mine in the world, employing over 1200 men and producing 100 tons of pig lead per day. There were during the years 1931 to 1936 the following number of cases of compensable lead poisoning: 1931, 69 cases; 1932, 95 cases; 1933, 77 cases; 1934, 1935 and 1936, 71 cases.

There were two hospitals (that of Mount Isa Mines, Limited, and the Mount Isa District Hospital) at which the patients were treated, probably about half the numbers in each. Pincus, who had been at Mount Isa from 1931 and was superintendent of the district hospital, commenced the use of sodium thiosulphate early in 1933, so his experience with this agent and previously with the then recognized methods of treatment was extensive.

There were in earlier years some very severe cases of permanent disability due to lead poisoning. In the later period from September, 1934, to the end of 1936, there were among the 68 cases four cases of very severe abdominal colic and vomiting, and two of extensor paralysis in addition to other disabilities. In the majority of cases the patients complained of less severe symptoms than those mentioned, such as abdominal pain (hypogastric and epigastric), constipation, muscular weakness, fatigue, loss of weight, headache, sleeplessness, metallic taste in the mouth, pains in the region of the joints (especially knees and elbows), pain in the back in the lumbar region, and cramping pain in the muscles, especially of the calves.

From September, 1934, onwards the cases were assessed by a medical board of three members. The present writer was not responsible for the treatment given, but as chairman of the board examined all patients and carried out investigations on the stippled cell counts, the ratio of monocytes *plus* large lymphocytes to small lymphocytes, the urinary lead concentrations, and any other appropriate tests on all of them.

In addition to the above-mentioned compensation cases there were numerous other employees who were suffering from milder symptoms of similar type, and who were (i) treated but remained at their previous work, which had caused their condition, or (ii) treated but transferred to other work of less hazardous nature, or (iii) not treated but merely transferred to work of a less hazardous nature.

In order to give some idea of the condition of the subjects, Table I gives a list of 16 cases at Mount Isa for which definite data are still available to the writer, and of two recent cases in Melbourne (Cases XII and XVIII).

The patients listed in Table I were all treated with sodium thiosulphate given intravenously (30 grains in a few millilitres of water on alternate days). In some of the cases it was the only treatment given. In some the colic was controlled at first with calcium given intravenously as the chloride or gluconate for one or more doses.

In one case (Case IX) the severe colic required morphine for a couple of days.

In a few of the cases a week or ten days had to elapse before the patient began to feel much improvement; but in the majority the improvement in the patient's clinical condition was rapid.

TABLE I.

Case Number.	Stippled Cells per 1,000,000 Red Cells.[1]			Ratio of Monocytes *plus* Large Lymphocytes to Small Lymphocytes	Urinary Lead Excretion. (Milligrammes per Litre.)
	Coarsely Stippled.	Finely Stippled.	Total.		
I	3050	1527	4580	0·965	0·19
II	1280	640	1920	1·07	0·48
III	5100	0	5100	0·94	
IV	720	1100	1820	1·20	0·134
V	2330	1370	3700	0·905	
VI	1250	0	1250	0·50	0·17
VII	480	1600	2080	1·66	
VIII	6400		6400	0·48	0·24
IX	—	100	100	1·45	0·18
					Several days after treatment commenced.
X	2530	0	2530	1·2	1·215
XI	1700	900	2600	1·48	0·23
XII[2]	4200	16,000	20,200	0·84	0·83
XIII	3940	2060	6000	1·5	0·32
XIV	—	—	—	1·9	
XV	210	0	210	0·75	0·19
XVI	1180	2880	4060	1·08	0·10
XVII	0	1450	1450	2·0	0·315
XVIII[3]	0	5400	5400	1·9	0·10

[1] For Cases XII and XVIII, stippled cell counts were made with a magnification of 900, all others with a magnification of 600. Cases XII and XVIII were Melbourne cases, and occurred in 1951 and 1941. Cases listed in this table do not necessarily represent the most severely poisoned subjects, but in Cases VI, VIII, IX and XII the patients were severely affected and in hospital. Case IX was one of severe abdominal colic and vomiting. In this case there were never more than 360 finely stippled cells per 1,000,000 red cells, although the blood was examined on several occasions; the patient was not very anæmic.

[2] Light field illumination, Seller's stain.

It was no part of the function of the medical board simply to remove from the lead hazard persons who were suffering from lead poisoning of a compensable degree and leave them without treatment, just as controls.

The assessment of the value of the method depends, therefore, to a considerable extent on the clinical judgement of the members of the board, and that opinion was that improvement under this method of treatment was definitely more rapid than could be accounted for by mere removal of the subject from the lead hazard.

Effect of Sodium Thiosulphate Therapy on Ratio.[1]

However, in order to give a numerical estimate of the improvement in condition a comparison has been made of the ratio of monocytes *plus* large lymphocytes to small lymphocytes before treatment began, and at a short interval afterwards. Ferguson and Ferguson (1934) and Shiels (1937, 1938, 1950) have already shown the value of this ratio as an indication of the clinical condition of persons who are suffering from lead poisoning, of those who are in the state of recovery or have just recovered from lead poisoning, and of those who have absorbed significant amounts of lead but are without symptoms of lead poisoning.

The tests were not carried out every day for any particular subject; in some instances a few days, in others a week or two, elapsed between tests, so that the intervals shown in column 7 are really greater than the actual intervals required to bring about improvement.

The *t* test of Fisher (1950)—that is, the ratio of the mean to the standard error of the mean—has been applied to the mean increase in the ratio. Its value was 6·919. When $n = 17$ (one less than the number of observations of the increase), this corresponds to a *P* value of less than 0·001. Thus there was a highly significant increase in the ratio shortly after commencement of the thiosulphate treatment.

In the cases considered in this paper the number of injections required to bring about a really satisfactory condition of well-being varied from two or three to a dozen or so.

The average ratio for these 18 subjects before treatment—namely, 1·23—was very close to that found for 65 cases of lead poisoning at Mount Isa—namely, 1·21.

[1] "The ratio" is that of monocytes *plus* large lymphocytes to small lymphocytes.

TABLE II.

Showing the Ratio for Each Subject Just Before Treatment Began and Again a Short Time Later.

1 Case Number.	1 Date.	3 Ratio on Date in Column 2.	4 Date.	5 Ratio on Date in Column 4.[2]	6 Increase in the Ratio.	7 Approximate Number of Days Since Treatment Began at which Ratio in Column 5 was Obtained.
I	3/ 4/36	0·97	14/ 4/36	5·30	4·33	11
II	15/ 5/36	1·07	18/ 5/36	3·20	2·13	3
III	23/ 2/36	0·94	5/ 3/36	3·82	2·89	11
IV	12/ 3/36	1·20	30/ 3/36	2·04	0·84	18
V	13/ 3/36	0·97	21/ 4/36	4·40	3·43	8
VI	21/11/34	0·70	27/11/34	3·88	3·18	6
VII	22/ 4/36	1·66	27/ 4/36	2·46	0·80	3
VIII	20/12/34	0·48	14/ 1/35	1·40	0·92	25
IX	23/ 1/35	1·45	28/ 2/35	2·20	0·75	5
X	21/ 5/35	1·20	18/ 6/35	4·90	3·70	28
XI	4/ 5/35	1·48	10/ 3/36	2·80	1·32	6
XII	8/ 6/51	0·84	18/ 6/51	4·20	3·36	10
XIII	12/ 5/36	1·50	26/ 5/36	2·35	0·85	14
XIV	3/ 1/36	1·90	16/ 1/36	3·80	1·90	13
XV[3]	12/ 2/36	0·75	9/ 4/36	2·90	2·15	56
XVI	12/ 5/36	1·08	18/ 5/36	2·05	0·97	6
XVII	26/ 5/36	2·00	15/ 6/36	2·40	0·40	20
XVIII[4]	8/ 2/41	1·90	10/ 4/41	3·84	1·94	21
Mean	—	1·227	—	3·219	1·992	—
Standard error	—	—	—	—	0·2879	—
					$t = 6·919$ P (for $n = 17$) $<0·001$	

[2] This subject had already had several injections when the test was performed on February 12, 1936. Only one test was performed between February 12 and April 10.

[3] In this case injections did not commence until March 20, 1941.

[4] At the time when the results shown in Column 5 were obtained, the subjects all showed very great improvement in their clinical condition, in many cases feeling very well indeed.

The average ratio after some days' treatment—namely, 3·22—approached the average value—namely, 3·72—for 109 persons at Mount Isa exposed to generally similar lead hazards, but without any symptoms or with very mild symptoms.

Comment.

Thus removal from work and a short course of thiosulphate injections changed the condition of subjects with lead poisoning almost into that of persons who had absorbed some lead but had no symptoms.

These facts are summarized in Table III.

Table IV shows the change in the distribution of the values of the ratio among the 18 subjects as a result of removal from work and treatment. Before treatment none of the values of the ratio exceeded 2, whereas the values of the ratio determined in some cases during treatment and in others at the end of the treatment exceeded 2 in all cases except one.

The improvement in clinical condition and in the ratio is not due merely to removal from work. This is shown by the facts that similar rapid clinical improvement occurred in the case of a person who had been away from work for over five months before the treatment started (Case XVIII, Tables I and II), and in the case of a number of persons with similar symptoms of a milder nature

TABLE III.
The Ratio.

Subjects.	Ratio.	Ratio.	Subjects.
18 persons with lead poisoning: before treatment.	1·23	1·21	65 persons with lead poisoning at Mount Isa.
The same 18 persons after some days' treatment.	3·22	3·72	109 persons at Mount Isa exposed to lead hazard but without lead poisoning.

than those shown by the subjects referred to in Tables I and II, who were treated while still remaining at work under the lead hazards which produced their symptoms.

Shortly after leaving work, the subject in Case XVIII had been treated with some improvement by the intravenous administration of calcium gluconate, vitamin *D* and a diet rich in calcium. When examined by the writer he still complained of weariness and lack of energy, the earlier improvement not having been maintained. After four injections he was feeling much better, and after several further injections (up to April 10, 1941) he was feeling very well indeed, and had no relapse.

TABLE IV.
Distribution of Values of the Ratio, Showing Number of Individuals Having Ratio within the Range of Values Set Out.

Range of Values of the Ratio.	Before Treatment.	During and After Treatment.
0 to 1·0 ..	7	0
1·1 to 2·0 ..	11	1
2·1 to 3·0 ..	0	8
3·1 to 4·0 ..	0	5
4·1 to 5·0 ..	0	3
5·1 to 6·0 ..	0	1

Summary.

1. The value of the intravenous administration of sodium thiosulphate in the treatment of acute and chronic lead poisoning has been discussed.

2. It has been shown that the treatment causes rapid improvement in clinical condition without recurrence of symptoms.

3. The treatment causes an increase in the ratio of monocytes *plus* large lymphocytes to small lymphocytes, which is highly significant statistically.

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SUPERFICIAL FUNGOUS INFECTION IN VICTORIA.

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THE object of this investigation was to establish a satisfactory method for the routine examination of suspected cases of superficial fungous infection and to find the relative frequencies of the various species in Victoria.

MATERIAL AND METHODS.

The patients were an unselected group examined in hospital and private practice. In the majority of cases the specimens were selected by myself after the suspected sites had been swabbed with methylated spirit. Vesicle tops and peeling skin, including the junction with intact skin, were selected from foot lesions and both broken hairs and scales from scalp lesions. Hairs were examined for fluorescence under filtered ultra-violet light. The specimens were placed in a drop of 5% aqueous caustic potash solution with glycerine (25%). They were allowed to stand for one hour without being heated to ensure clearing of the material and were examined microscopically within the next hour. The advantages of this solution were that drying out did not occur even if the specimens were left for twenty-four hours for further examination, and that culture of the fragment could be carried out subsequently (at least after an interval of up to two hours) with a high percentage of successful results.

Cultures were carried out as follows: (*a*) with dextrose (4%), peptone agar plates incubated at 30° C.; (*b*) fluid culture in a specially designed cell in an atmosphere saturated with water vapour and at a temperature of 30° C. The cell was a modified Van Tieghem cell, the component parts being a glass slide three inches by one and a half inches in area, a cover slip one and a half inches by one and a half inches in area, and a stainless steel ring, 3·0 centimetres in diameter, 0·3 centimetre high, and 0·2 centimetre thick. The cell is formed by sealing slide, steel ring and cover slip with paraffin wax. The cell rests on a U-shaped glass rod closely fitted in a Petri dish, the floor of which is covered with moistened filter paper. The culture fluid consists of dextrose (4%), agar (0·15%) and peptone (1%) with penicillin and streptomycin added in a concentration of 50 units of each per millilitre to inhibit bacterial growth (Kligman and Rebell, 1949). The steel ring is immersed in a beaker of heated paraffin wax and applied to the sterilized slide and adheres on cooling. The cover slip rests on the ring, and one drop of the culture medium is placed on the centre of the cover slip. The drop is inoculated with the specimen, and the cover slip is reversed and then sealed to the ring by means of a heated glass slide.

RESULTS OF INVESTIGATION.

Two hundred and thirteen patients with lesions commonly attributed to fungi were investigated. The lesions were examined microscopically and culturally and the tests were repeated on numerous occasions when the results were negative. One hundred and twenty of these cases were proved to be of fungous ætiology, and of these 114 gave positive results both microscopically and culturally, and six gave positive results microscopically, but no pathogenic fungus could be grown on culture. In no case was a pathogenic fungus grown on culture in the absence of positive microscopic findings.

Of the 93 cases in which the microscopic and cultural findings were negative, there were 32 cases in which an inability to perform repeated tests after cessation of fungicidal treatment did not eliminate the possibility of a fungous infection, and there were 61 cases in which repeated tests in the absence of fungicides and the subsequent progress of the patients reasonably excluded a fungous causation.

The close relationship between cultural and microscopic findings found in this investigation is apparently unusual. It was possibly due to (*a*) personal selection of the specimens to be examined in most cases, (*b*) the performance of repeated tests in the absence of fungicides in clinically suspect cases, (*c*) culture of the fragment of specimen in which mycelium was seen microscopically, (*d*) fluid culture in a cell saturated with water vapour as well as culture by conventional methods.

Marples and Di Menna (1949) found in their investigation of fungous infection of students in Otago that of 60 positive cultures 26 were found in cases in which no mycelium was found on direct microscopic examination. Of 37 cases in which mycelium was found on direct microscopic examination, 18 gave negative cultural results.

Linn and Magarey (1941), in their investigation of fungous infections of the feet in a military camp, found six cases with positive microscopic findings out of 251 cases with abnormal clinical findings, and in none of these cases was a positive culture obtained. From 211 cases with normal or doubtful clinical findings four positive cultures were obtained, although no mycelium was seen on microscopic examination. It is probable that the small number of positive cultures was in part due to the discarding of cultures at the end of ten days, and in part due to recent fungicidal treatment.

Broyles *et alii* (1945) found that of 154 cases in which mycelium was found on microscopic examination, in only 17 (11%) could a culture be obtained.

Hulsey and Jordan (1925) found that of 47 cases in which mycelium was found on direct microscopic examination, in only five were positive results obtained on culture.

Legge, Bonar and Templeton (1929) obtained 5% to 6% of positive results on culture.

It will be seen, however, from the investigation reported here that diagnosis of fungous infection can adequately be made by microscopic examination alone if provision is made for repetitions of the examination. Cultural methods did not increase the percentage of positive findings but were necessary to determine the type of fungus present.

Species of Fungi in Different Sites.

Scalp.

Scalp infections were confined to children from the ages of two to twelve years, with the exception of one adult female aged about sixty years. Boys comprised about 60% of the children affected and the majority of the patients resided in urban districts around Melbourne. Of 68 positive cultures obtained from cases of *tinea capitis*, *Microsporum lanosum* was found in 46 and *M. audouini* in 19, and in both these species the affected hairs showed a bright green fluorescence under filtered ultra-violet light.

It is interesting to note that all the patients with *M. lanosum* infection were cured within three months of the commencement of supervised local treatment, while the *M. audouini* infections were still active after six months of local treatment. From a kitten and a puppy each suspected of infecting humans *M. lanosum* was easily cultured from fluorescent hairs. The cultures of *M. audouini* were of the form described by Duncan as the "dysgonic" type and reported by Jacqueline Walker (1950) as comprising 15% of cultures of this species in Great Britain. This form may be overlooked, as the initial growth sometimes develops only on the fragment of infected hair which forms the inoculum, and although straggling hyphæ may later pass into the depth of the agar or spread thinly on its surface, yet no good mycelial bed is formed. In parasitic life in the hair the "dysgonic" type of *M. audouini* is apparently not distinguishable from the normal type. In no case has the normal or "eugonic" form been isolated.

The remaining three cultures revealed an endothrix trichophyton with large spores in chains inside the hair. The species in each case was *Trichophyton sulphureum*, stated to be common in Australia (Gohar, 1948). The hairs in these three cases showed no definite fluorescence with filtered ultra-violet light. The source of these infections is unknown and the course is chronic.

Feet.

The subjects with infected feet were adults, and there was a preponderance of males. Of positive cultures obtained, eight were of *Epidermophyton floccosum* and the remaining 30 were separated into two groups—*T. gypseum* and *T. purpureum*—on the basis of lack of development or development of a reddish-purple pigmentation on dextrose peptone agar plates. This placed 23 in the *T. gypseum* group and seven in the *T. purpureum* group.

This shows a rather lower proportion of *T. purpureum* infection as compared with the results of other workers. The differentiation of highly pigmented strains of *T. gypseum* from those of *T. purpureum* is difficult. Bocobo and Benham (1949) found some strains with the morphological characteristics of *T. gypseum* which acquired the rose-purple pigmentation of *T. purpureum*, and the problem is further complicated by the fact that some strains of *T. purpureum* may lose their ability to produce a rose-purple pigmentation after repeated subculture. It was not found possible to differentiate *T. gypseum* and *T. purpureum* by culture at room temperature on 2% dextrose corn meal agar plates, as described by Bocobo and Benham (1949). It is possible that this was due to use of local (maize) corn meal, and further investigations are proceeding.

Glabrous Skin.

Of seven cultures obtained from lesions of the glabrous skin, where no other site was involved, from six *M. lanosum* was obtained and from the remaining one *T. faviforme*. A similar fungus was cultured from a case of ringworm in a cow, and examination of the affected hairs revealed sparse chains of large spores outside the hair. Fowle and Georg (1947) found a faviforme trichophyton—*T. discoides*—the most frequent cause of inflammatory ringworm in Iowa, a farming State.

Beard.

There was one case of *tinea barbæ*. Investigation revealed an ectothrix infection, and *T. purpureum* was grown on culture.

Nails.

Of a number of suspected ringworm infections of the nails, in only one could mycelium be seen with certainty, and in this case *T. purpureum* was grown on culture. In no other case was a positive culture obtained.

An investigation of nail affections is being carried out.

SUMMARY.

Microscopic examination and culture were carried out in a series of 213 cases of suspected fungous infection.

It was found that culture methods did not increase the proportion of proved cases of fungous infection. A closer relationship than is usually reported was found between cultural and microscopic findings. The probable reasons for this are discussed.

Cultural methods indicate the great preponderance of *M. lanosum* infections of the scalp in children and its presence in domestic animals, the existence of some resistant cases of scalp infection associated with the human type of fungus, *M. audouini*, and the existence of some cases of non-fluorescing ringworm of the scalp, of which the source of infection is obscure.

Cultural methods indicate the types of fungi found in cases of *tinea pedis*, and in so far as the great majority of subjects are ex-servicemen, show the extreme difficulty in eradicating infection in this site. It would appear that after a course of treatment repeated microscopic tests should be made before claim of cure is justified.

ACKNOWLEDGEMENTS.

This investigation was carried out at the Alfred Hospital under a grant from the Sol Green Trust and is being continued. The identification of the cultures of the "dysgonic" form of *M. audouini* was kindly confirmed by Dr. Jacqueline Walker, of the Mycological Reference Laboratory at the London School of Hygiene and Tropical Medicine. My thanks are due to Mr. Christie, of the Pathology Department of Saint Vincent's Hospital, for his great assistance in the design of a satisfactory cell culture chamber. The help and encouragement of the staff of the Pathology Department of the Alfred Hospital are gratefully acknowledged.

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ADMINISTRATION OF CORTISONE BY THE AEROSOL METHOD IN THE TREATMENT OF BRONCHIAL ASTHMA.

By CLARENCE M. MARSHALL,
Melbourne.

FOUR patients suffering from bronchial asthma were treated with cortisone by inhalation according to the method of treatment devised by M. L. Gelfand (1951).

The preparation of the aerosol solution is as follows. One millilitre of "Cortone" (Merck) containing 25 milligrammes of cortisone acetate was diluted with four millilitres of physiological salt solution. The patients were instructed to aerosolize one millilitre of this mixture with a nebulizer every hour, beginning at 9 a.m. and ending at 10 p.m. Thus five milligrammes of cortisone were applied directly to the tracheo-bronchial tree in ten doses, a total of 50 milligrammes daily. Treatment was continued for two weeks.

CASE I.—Mrs. B.M., aged thirty-five years, had suffered from bronchial asthma for twenty-two years, and in that period had experienced severe *status asthmaticus* attacks. A course of treatment with the above solution commenced on January 20, 1952, during a *status asthmaticus* attack, after a trial of many of the usual therapeutic agents, including ACTH, had failed to relieve the attack.

The treatment with cortisone was continued for twelve days, and after four days all signs of bronchospasm had disappeared. Six weeks later she was still free of symptoms and signs—the longest period in her memory.

CASE II.—Mr. G.S., aged twenty-six years, an asthmatic of twelve years' duration, was given a course during an attack. Almost all signs had disappeared after three days of treatment. Relapse occurred five days after cortisone therapy was stopped. Readministration of the hormone again produced amelioration of symptoms.

CASES III AND IV.—Miss L.K., aged thirty years, and Mrs. E.J.C., aged fifty-nine years, responded favourably after the fourth day of treatment. A mild relapse occurred with Miss L.K. three weeks after cessation of treatment. Mrs. E.J.C. ten weeks after cessation of the "Cortone" treatment has had no recurrence of symptoms.

The cortisone dosages used by the aerosol method in this study were considerably lower than dosages used in asthma when the hormone is given intramuscularly or orally. Perhaps better absorption takes place when cortisone is given by the aerosol route.

There was no prolonged irritation of the tongue or throat during treatment, although at the start in three of the cases increased coughing and slight hoarseness developed. These symptoms disappeared when the amelioration of the asthmatic condition became evident. None of the minor physiological side effects or major signs of hypercortisonism were encountered in any of the patients.

It is believed that cortisone acts on the tissue level. In discussing the mechanism of cortisone's action when applied directly to the bronchial mucosa in asthma, Gelfand states: "The direct application of cortisone to the bronchial mucosa by the aerosol method in bronchial asthma may either interfere with the union of antigen and antibody or inhibit the liberation of histamine at the site of its shock organ . . . . Another possibility is that since the pulmonary epithelium offers a good absorptive area the cortisone delivered to it by this method enters the bloodstream and exerts its beneficial effect systemically at the tissue level."

The author recommends that further studies with the aerosol method of cortisone administration be done, since this method is simple and permits the use of cortisone in asthma without undesirable side effects.

Reference.

Gelfand, M. L. (1951), "Administration of Cortisone by the Aerosol Method in the Treatment of Bronchial Asthma", *The New England Journal of Medicine*, Volume CCXLV, page 293.

Reports of Cases.

MEDITERRANEAN ANÆMIA: REPORT OF THREE CASES.

By A. H. TEBBUTT,
Sydney.

UNDER the eponym of Cooley's anæmia, Baker and O'Neill (1951) have recently published a case of this disease in its severe form in an infant, the congenital red cell trait being apparently homozygous, for both parents showed it and were of Sicilian origin. The paternal grandparents also presented the red cell abnormalities. Previous case reports in Australia were limited to those by Sinn (1949) and myself (1950). I have already stated that with much migration from the Mediterranean basin into Australia the syndrome will be met with if borne in mind. I have since met with three examples, and publish them to show that abnormalities of the blood picture, and in particular lowering of the colour index, the calculated mean corpuscular volume and mean corpuscular hæmoglobin without a fall and even a rise in the red cell figures, may be due to the red cell abnormality of Mediterranean anæmia, though some of these patients may show no clinical signs or symptoms of anæmia. They appear to be well adapted to the lowered hæmoglobin value. It should be stated that these were routine blood examinations with the use of venous oxalated blood, and that the red cell fragility tests were performed on the same day by the addition of one drop to graded salt solutions, a specimen of normal blood taken on the same day being used as a control.

Case I.

The patient was a woman in the fourth decade, whose parents were both northern Italians. A routine blood examination was carried out on her prior to operation for scoliosis in decompensation. The results of the blood examination were as follows. The red blood cells numbered 5,100,000 per cubic millimetre, the hæmoglobin value was 11·7 grammes *per centum*, and the colour index was 0·76. The hæmatocrit reading was 35%, the calculated mean corpuscular volume was 70 cubic μ, the mean corpuscular hæmoglobin was 23 micromicrogrammes, and the mean corpuscular hæmoglobin concentration was 33%. These figures disclose an increase in red cell numbers for a woman in spite of a lowered hæmoglobin value and a lowered hæmatocrit reading. In stained films most red cells show some central pallor; many are target cells; there are also many elongated oval cells and a few poikilocytes. Some red cells appear to be normal. There are very few stippled red cells and polychromasic cells; no nucleated red cells were found. Platelets were not reduced in numbers. The leucocytes numbered 5,700 per cubic millimetre, and the differential count revealed no abnormality and no neutrophilia (57%). The red cell fragility test (osmotic fragility) revealed hæmolysis commencing in 0·37% sodium chloride solution and not complete in 0·2%. A test on normal control blood showed, in the same saline solutions, hæmolysis commencing at 0·4% and complete at 0·3%.

Case II.

A man, aged forty-one years, brother of the first patient, had no complaints as to his health, and his blood had not been previously examined. The findings in his blood were as follows. The red cells numbered 6,100,000 per cubic millimetre, the hæmoglobin value was 14·7 grammes *per centum*, and the colour index was 0·8. The hæmatocrit reading was 43%. The calculated mean corpuscular volume was 70 cubic μ, the mean corpuscular hæmoglobin was 24 micromicrogrammes, and the mean corpuscular hæmoglobin concentration was 34%. When allowances are made for normal quantitative sex differences in red cell numbers and hæmoglobin values, the qualitative figures are almost identical in brother and sister. In stained films there is central pallor, and target cells, oval cells, poikilocytes and polychromasic cells are present. The leucocytes numbered 9000 per cubic millimetre; there was no neutrophilia (50%), but there was an increase in the proportion of monocytes (16%). An osmotic fragility test revealed hæmolysis commencing at 0·37% sodium chloride solution and not quite complete at 0·2%. A test on normal control blood revealed hæmolysis commencing at 0·45% and complete at 0·3%.

Case III.

The patient was a man of middle age, whose father and mother were both Greek and whose blood was examined in a routine investigation on account of pains in the legs thought to be arthritic in origin. The blood examination gave the following results. The red blood cells numbered 5,400,000 per cubic millimetre, the hæmoglobin value was 13·5 grammes *per centum*, and the colour index was 0·83. The hæmatocrit reading was 41%, the calculated mean corpuscular volume was 76 cubic μ, the mean corpuscular hæmoglobin was 25 micromicrogrammes, and the mean corpuscular hæmoglobin concentration was 33%. Here again, though the red cell number is slightly above the mean for adult males (the count was repeated a week later and made 5,300,000 per cubic millimetre), yet the hæmoglobin value was well below the mean value for males (a week later it was estimated at 12·3 grammes *per centum*), and the hæmatocrit reading was slightly below. The findings are therefore a mild microcytic anæmia with a lowered colour index and a lowered mean corpuscular hæmoglobin. In stained films the changes were not pronounced, but some anisocytosis was present and a few microcytes and oval cells, a very few target cells, a few polychromasic cells, and one stippled red cell were seen. The leucocytes numbered 6600 per cubic millimetre and there was no neutrophilia (54%). Hæmolysis in an osmotic fragility test began at 0·4% sodium chloride solution and was complete at 0·24%. A test on normal control blood revealed in the same saline solutions lysis commencing at 0·4% and complete at 0·3%. In this case the results gave only a suggestion of increased fragility.

Comment.

By whatever name this congenital and familial blood dyscrasia comes to be generally or finally known—Cooley's anæmia, Mediterranean anæmia, target oval-cell anæmia,

thalassæmia *et cetera*—it will probably be classified with the hæmolytic anæmias as at present. In a recent review of hæmolytic anæmias Eric Ponder (1951) states that very little is known about the process which destroys these red cells; but Ashby curves show that an intrinsic defect is present, at least in some cases, which makes them short-lived. Just as lysis is correlated with the spherical form as in spherocytic anæmia, so fragmentation is with the discoidal leptocytic form. Fragmentation of the very flat disks of Mediterranean anæmia is a conspicuous phenomenon and may be the method of their destruction. Ponder also states that intrinsic defects of structure seem to be accompanied by peculiarities in the contained hæmoglobin.

Summary.

Three cases of Mediterranean anæmia in its milder, probably heterozygous, form are briefly reported.

Acknowledgements.

I am indebted to Dr. Stuart Scougall and to Dr. O. A. Diethelm, both of Sydney, for kind permission to publish these notes of cases referred to me for hæmatological investigation.

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Reviews.

ARTHRITIS AND RHEUMATIC DISEASES.

"ARTHRITIS AND THE RHEUMATIC DISEASES", by Philip Lewin, is written for the layman.[1] The nervous, tired, anæmic adult, who was delicate and hard to rear as a child, is told that he is already suffering from rheumatoid arthritis. "Indigestion, constipation, fatigue and susceptibility to illness are evidence that arthritis is already present in your body." A medical man will find it difficult to accept these statements, but they will undoubtedly convince many people that they have arthritis. The statements that the sacro-iliac joints are "the hinge between your legs and your back" and that the cervical spine is "the vertebræ just below your neck" make strange reading to anyone who has studied anatomy. One doubts whether it is wise or kind to inform the sufferer from ankylosing spondylitis that he might eventually walk with his "curved back almost parallel to the ground, like a bear on all fours". The advice given to patients suffering from arthritis as to what they themselves can do for their illness in regard to diet, rest, exercise and posture is sound, and it would be better if the subject matter of the book was confined to such advice.

IONIC INTERACTIONS IN LIVING MATTER.

"A TEXTBOOK OF GENERAL PHYSIOLOGY", by Hugh Davson, D.Sc., is a book of 659 pages, well produced with excellent diagrams, tone plates and bibliography.[2] It is divided into six parts: "The Structural Basis of Living Matter", "Transformation of Energy in Living Systems", "The Transport of Water and Solutes", "Characteristics of Excitable Tissue", "The Mechanism of Contraction of Muscle", and "Effects of Light".

These divisions appear to provide ample opportunity to include the important topics of general physiology, but the reader will look in vain for any systematic consideration of the circulation of blood or other body fluids, gaseous exchange of animals with the environment, or organization and integration of activities by nervous or humoral mechanisms. Even enzymic mechanisms are not dealt with in a general comprehensive manner; there are some general formulations about these systems under the heading of photodynamic action.

The book is not therefore a text-book of general physiology, but it is an excellent book on many aspects of ionic interactions in living matter. If the author were to cut out the matter irrelevant to this topic and include all relevant matter he would with small trouble produce a most valuable treatise. In doing this he would need to be careful to discard completely notions now disproved. It is not very profitable to read at length considerations based on the notion that the cell membrane is impermeable to sodium when the same page records that the cell is permeable to sodium.

All the material presented is set out clearly. Occasionally terms are used in an irregular way; for example, on page 108 a living organism is "in a higher state of potential energy than when it is dead". Rarely is the reasoning not clear, but it is hard to see on page 122 why a high body temperature is of value in permitting the regulation of heat loss. Similarly on page 149 a membrane is said to be necessary to prevent two aqueous media from mixing: gelatin cubes without membranes get along quite well in certain salt solutions. There is a misstatement of mM for mEq. on page 242, but the quantitative material presented appears to have been checked thoroughly.

Every serious student of physiology will be grateful to the author for this book, even though it is not according to label.

[1] "Arthritis and the Rheumatic Diseases", by Philip Lewin, F.A.C.S., F.I.C.S., with a foreword by Morris Fishbein, M.D.; 1951. New York: McGraw-Hill Book Company, Incorporated. 8½" × 6", pp. 190. Price: $3.50.

[2] "A Textbook of General Physiology", by Hugh Davson, D.Sc. (London); 1951. London: J. and A. Churchill, Limited. 9¼" × 6½", pp. 672, with 288 illustrations. Price: 45s.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Pathology of the Cell", by Gordon Roy Cameron, M.B., D.Sc. (Melbourne), F.R.C.P., F.R.S.; 1952. Edinburgh: Oliver and Boyd. 10" × 6½", pp. 856, with 64 plates and 41 text figures. Price: £4 4s.

An inquiry into "the foundations of cellular theory in general and of cell pathology in particular".

"Cold Injury: Transactions of the First Conference, June 4-5, 1951, New York", edited by M. Irené Ferrer; 1952. New York: The Josiah Macy Junior Foundation. 9¼" × 6½", pp. 248, with 39 illustrations, two in colour. Price: $3.25.

Contains papers and discussions on animal studies, hypothermia, homœokinesis and acclimatization.

"Cybernetics: Circular Causal and Feedback Mechanisms in Biological and Social Systems: Transactions of the Eighth Conference, March 15-16, 1951, New York", edited by Heinz Von Foerster, associate editors, Margaret Mead and Hans Lukas Teuber; 1952. New York: The Josiah Macy Junior Foundation. 9¼" × 6½", pp. 260, with 11 text figures. Price: $4.00.

Contains papers and discussions on the following subjects: communication patterns in problem-solving groups; communication between men and the meaning of language; communication between sane and insane and hypnosis; communication between animals; presentation of a maze-solving machine; "in search of basic symbols".

"A Course in Practical Therapeutics", by Martin Emil Rehfuss, M.D., F.A.C.P., and Alison Howe Price, A.B., M.D.; Second Edition; 1951. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 11½" × 9", pp. 956, with 96 illustrations. Price: £8 1s. 3d.

Revised with the addition of much new material since the first edition was published in 1948.

"A History of Neurological Surgery", edited by A. Earl Walker, M.D.; 1951. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 10½" × 7½", pp. 596, with 152 illustrations. Price: £6 9s.

Elaborated versions of essays presented in seminars by members of the Division of Neurological Surgery of the Johns Hopkins University.

The Medical Journal of Australia

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All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: surname of author, initials of author, year, full title of article, name of journal without abbreviation, volume, number of first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

ANTIBIOTICS AMOK.

. . . some of the inventions already known are such as, before they were discovered, it could hardly have entered any man's head to think of; they would have been simply set aside as impossible. For, in conjecturing what may be, men set before them the example of what has been, and divine of the new with an imagination preoccupied and coloured by the old; which way of forming opinions is very fallacious; for streams that are drawn from the spring-heads of nature do not always run in the old channels.

THESE words were written by Francis Bacon and are quoted by René J. Dubos in his important book published in 1945 and called "The Bacterial Cell in its Relation to Problems of Virulence, Immunity and Chemotherapy". Dubos quotes them in his chapter "Bacteriostatic and Bactericidal Agents" over the section in which he deals with chemotherapeutic agents. He points out, as must be well known to all of us, that of the countless antimicrobial substances produced by chemical methods or extracted from biological materials, only a very few can be used in the prevention and therapy of infectious diseases. It is thus of the greatest importance to know what property or combination of properties is required to endow a substance with chemotherapeutic activity. The ideal chemotherapeutic agent is obviously (in Dubos's words) one which exhibits great affinity for the parasites but which is completely inactive against the constituents of the tissues of the host. But we know that most antimicrobial agents, of either synthetic or biological origin, affect all kinds of living cells, reacting with morphological structures or with metabolic systems common to all living matter; in other words, they behave as general protoplasmic poisons. There are many factors which influence the selectivity of an antimicrobial agent. Dubos includes amongst the attributes which bear a definite relation to susceptibility, the acidic and basic properties of the cell under consideration, the nature and property of its membrane, its permeability, the relative importance for metabolism and viability of the specific biochemical systems affected by the antimicrobial agent, the activity of the autolytic enzymes and so on. He points out that each of these properties can undergo variation, either independently or simultaneously, and thus give rise to mutant forms of modified susceptibility. Medical practitioners have during the last few years witnessed the discovery and development of antibiotic preparations and their application to the diseased tissues of the human body. It is salutary to pause and to remember that for every effective antibiotic preparation put on the market many hundreds have been discarded on account of their toxic reactions or for some other reason. It is not surprising if medical practitioners have been avid in making use of tried and proven antibiotic preparations. Indeed, as we know something of human nature and of man's readiness to avail himself of any help in time of need, we need not be surprised that antibiotics have been and are being used far and wide without just reason. It may truthfully be said in this regard that therapy has run amok. Every civilized country at the present time has what may be called its antibiotics problem. This statement has recently been made by Dr. L. R. Mallen, who has just returned to Australia from a council meeting of the World Medical Association. The point is that, in their desire to cure quickly an infection which threatens the life of a patient, doctors forget that when they use a powerful drug it has an effect not only on the specific organism whose destruction is aimed at, but also on the other organisms and on the cells of the body. Some of the organisms affected are included in the normal flora of the body. While it is not necessary to discuss this point in detail, it may be useful to recall that the use of sulphonamides may interfere with the absorption of vitamins from the intestine. The overuse of antibiotics, and indeed of any other specific and quickly acting preparation, has thus a profound action on the body of the patient. It has another, and perhaps more subtle effect, and that is the substitution of, or shall we say the reversion to, a rule of thumb therapy which sets accurate diagnosis on one side and empiricism on a pedestal, undermining the scientific basis of medicine and the practitioner's ability to use it.

The discussion of the New South Wales Branch of the British Medical Association on the use of antibiotics reported in this issue is opportune. It is common knowledge that the introduction by the Commonwealth Government of the *Pharmaceutical Benefits Act*, according to the provisions of which certain costly drugs, described as life-saving, have been supplied to patients on the prescription of a medical attendant free of charge, was followed by an enormous increase in the quantities of antibiotics used. The Government could not view this increase with equanimity on account of the sharply rising costs; and the recent determination of the Government, on account of the general financial emergency, to reduce the quantity of goods allowed to be imported has brought the matter to a head. If, as a result, the medical profession displays a more scientific attitude of mind than has lately been in evidence, some good will have been achieved. At the New South Wales Branch meeting, Dr. F. H. Hales Wilson stated the position clearly in an opening paper, and Dr. E. F. Thomson reported interesting work which had been carried out at the Royal Prince Alfred Hospital, Sydney. He showed that in that hospital there had been a rising incidence of antibiotic-resistant strains of certain micro-organisms since the introduction of antibiotic therapy. We

can accept his statement that the facts recorded by him represent the state of affairs in the majority of large hospitals. He laid stress on the fact that adequate bacterial examination and adequate antibiotic sensitivity tests are essential whenever they are practicable. This raises several questions, and one of these is whether clinical bases can be determined for the selection of patients for antibiotic therapy. This question has been debated by Waldo E. Nelson.[1] Nelson referred to what he termed indiscriminate antimicrobial therapy of diseases presumed to be infectious in origin, and he enumerated several reasons which had been advanced in favour of this indiscriminate treatment. He pointed out, however, that the arguments against this type of therapy far outweigh those in favour of it. These arguments are so important that they should be stated. They are six in number. (i) A great economic loss takes place, since either the majority of patients treated are not benefited by the therapy or the benefit is so minimal as not to justify the expense and effort involved. (ii) Unnecessary therapy has a detrimental effect on the layman, either making him feel falsely dependent on a therapeutic agent or making him sceptical of all therapeutic endeavour. (iii) Indiscriminate antimicrobial therapy may lead to increased bacterial resistance to available antimicrobial agents. (iv) Indiscriminate antimicrobial therapy results in a less critical attitude on the part of the physician towards diagnostic and therapeutic endeavour. (v) There is an increasing frequency for varying degrees of suppression of disease to occur without cure; this results in severe, chronic, disabling disturbances which often have a fatal outcome, particularly in conditions affecting the meninges, pleura and bones. (vi) There are no substantial data to indicate that the serious consequences of pyogenic complications cannot be avoided by appropriate therapy instituted at the onset of their clinical appearance in infections which are initially viral in origin. Nelson asks whether the busy practitioner can evolve a working policy in regard to antimicrobial therapy which is in line with current knowledge and which is applicable for home and hospital patients. He writes that the answer is undoubtedly "no", if one expects a policy which is applicable to all cases, but that it is "yes" if a working basis is accepted which is infinitely more satisfactory than the policy of "treat, and if the patient does not get well, attempt to diagnose". Nelson discusses in turn infections of the upper respiratory tract, infectious disturbances of the gastro-intestinal tract, and pyogenic infections of the urinary tract. His views on the application of antibiotic therapy to these conditions cannot be reproduced in this place; his paper is worthy of study from this point of view. A second point in Dr. Thomson's paper to which attention should be drawn has to do with sensitivity control tests. This question is dealt with in an editorial in the journal which contains the article by W. E. Nelson. Here references are made to many contributions to the literature and the conclusion is reached that there are many pitfalls in the application of sensitivity tests to the clinical control of antibiotic therapy. Further refinements of technique and correlation of clinical and laboratory results are stated to be necessary before the total picture can be clarified. Reference is made to a contribution by G. G. Jackson and M. Finland.[1] These authors regard sensitivity tests, as performed in the ordinary clinical laboratory, as only general qualitative guides which distinguish susceptible from non-susceptible organisms. Even this distinction may not be made by the ambiotic disk method, unless the proper range of antibiotic concentrations is employed. Jackson and Finland believe that it is much more important to determine the ætiological agent accurately than to perform routine sensitivity tests. G. H. Spaulding and T. G. Anderson, in a paper on "The Selection of Antimicrobial Agents by Laboratory Means"[2] describe the disk method for determining susceptibility to antibiotics, and state that the procedure is so simple as to be within the scope of any laboratory capable of culturing clinical material. Another important aspect of this subject was dealt with in the Sydney discussion by Dr. Phyllis Rountree—cross-infection. This is a fascinating aspect of the subject. In a recent editorial[3] the cross-resistance to antibiotics is discussed. The view is expressed that the proof that bacteria rendered resistant *in vitro* may exhibit cross-resistance to one or more other antibiotics may help in elucidating the mode of action of antibiotics. If the antimicrobial action of antibiotics is due to an interference with one or more of the bacterial enzyme systems, those agents that show cross-resistance may exercise their action along common pathways. It is pointed out that there is some evidence that cross-resistance to antibiotics may develop during therapy, though in such studies it is not easy to exclude superinfection with resistant strains. The editorial concludes with the statement that should the effects noted *in vitro* also obtain *in vivo*, the possibility of developing cross-resistance, with subsequent lessening of the efficiency of antibiotic therapy, should be a deterrent to the indiscriminate use of antibiotics, particularly those that readily give rise to resistance. Another point of practical importance is the fact that moniliasis may occur in patients who have been treated with aureomycin. This is mentioned in his paper by Hales Wilson, who also reproduces the announcement made by the Council on Pharmacy and Chemistry of the American Medical Association in regard to the labelling of aureomycin, chloramphenicol, and terramycin. In this regard, attention may be drawn to a paper by R. B. Tappenfort and E. S. Schnall,[4] who adduce clinical and laboratory evidence that aureomycin stimulates the growth of *Candida albicans*. They have carried out observations on 16 patients in whom lesions or symptoms resembling those of moniliasis occurred. These patients had been treated by aureomycin and in every instance a yeast-like fungus was found by examination of a slide and/or *Candida albicans* was obtained by culture. It was found that aureomycin hydrochloride in 250-milligramme capsules which had been prepared for oral administration stimulated the growth of monilial organisms *in vitro*. It was concluded that the growth-stimulating factor of the aureomycin preparation was probably not the same as the antibiotic factor. An explanation for the increased incidence of moniliasis among

[1] *The Journal of the American Medical Association*, December 1, 1951, page 1340.

[1] *A.M.A. Archives of Internal Medicine*, October, 1951, page 446.

[2] *The Journal of the American Medical Association*, December 1, 1951, page 1336.

[3] *The Journal of the American Medical Association*, February 9, 1952, page 470.

[4] *A.M.A. Archives of Internal Medicine*, December, 1951, page 729.

patients treated with aureomycin hydrochloride was thought to be the possibility that the growth factor is active *in vivo*.

The foregoing brief references to what may be called the laboratory side of the question, together with the New South Wales Branch discussion, should convince readers that much more requires to be learned about these powerful drugs known as antibiotics. This factor must be borne in mind continually; if this is done we shall not have to worry about what we have called the more subtle side of the picture. At the Sydney discussion, E. F. Thomson was more forthright than he is in the printed version of his paper. He made it quite clear that it was not only certain resident medical officers who were given to the excessive use of antibiotics, but that many seniors were just as bad. It has also been claimed that practitioners sometimes yield to the importunities of the referring practitioner or of the patient and his relatives. Apparently some resident medical officers do not know that there was a pre-antibiotic era in which patients recovered from infective processes without the use of antibiotics, and offending seniors, who know it perfectly well, close the door of their memories. Or so it would appear. In surgical practice there are no doubt some cases in which the pre-operative use of antibiotics may be justified. It is difficult, however, to defend their use before operation in what is commonly described as a "clean" surgical case. Surgeons who do this should study again the history of surgery. They need to learn once more that Lister's discoveries were followed by the development of aseptic surgery and that when Nature is left to herself she can finish the healing process. Those who use antibiotics unnecessarily before the performance of a surgical operation are, as it were, harking back to the days of Lister. Lister *redivivus*! There is no doubt whatever that continued reliance on antibiotics as a routine measure would ultimately impair the aseptic technique of surgery. E. F. Thomson used a happy phrase when he referred to "universal antipyretics". The first thing of which some practitioners think when a patient has a rising temperature, and the cause is not at once apparent, is to order an antibiotic. Reports are not infrequent that practitioners will refer patients to hospitals or consultants with the statement that the patients have received one or more of the antibiotics, that no improvement has resulted, and that the practitioner would like the hospital or consultant to investigate the condition, clearly indicating that he himself has done nothing of the kind. Our use of the words "subtle danger" is undoubtedly justified.

Current Comment.

NEOPLASMS OF THE KIDNEY AND URETER.

Among neoplasms those of the kidney have many distinctive features and present their peculiar problems both to the clinician and to the pathologist. William Boyd, in his book on surgical pathology, describes the study of kidney tumours as "one of the most perplexing and confusing chapters in the whole of pathology", and the clinician experienced in this field will echo the sentiment from his own viewpoint. Tumours of the renal pelvis and ureter are rare and any sizable series must attract attention. For these and other reasons there is much interest to be found in a study by E. W. Riches, I. H. Griffiths and A. C. Thackray[1] of 2314 newgrowths of the kidney and ureter. The series was collected from members of the British Association of Urological Surgeons working in 67 centres in the British Isles during the period from 1935 to 1950; its collectors believe it to be the largest series ever described. The classification adopted is simple: adenocarcinoma, in which are included both clear and granular-celled tumours of the Grawitz type, accounts for 75% of the total; Wilms tumours make up 8%; transitional-cell carcinoma of the renal pelvis comprises 7%; squamous-cell carcinoma of the pelvis 2·5% and simple pelvic papilloma 3%; primary neoplasms of the ureter make up 0·9%; the remaining 1·9% consists of tumours not readily classifiable from the available data. It is interesting to note that hæmaturia occurred in association with 62% of the adenocarcinomata, and with about 90% of the papillary transitional cell tumours, whether malignant or benign. It accompanied only 18% of the Wilms tumours, but with these the predominant feature was a large tumour; with growths of the renal pelvis a notably sized tumour was rare. Renal pain was fairly frequent in every group, but met least in the Wilms tumour group.

Particular attention is given to the question of survival in each of the groups of neoplasms. In cases of adenocarcinoma it seems that women are the longest survivors. A well-known feature of adenocarcinoma is that it may be discovered during a search for a silent primary lesion responsible for symptomatic metastases, the outlook in such cases being poor; of 56 cases of this type recorded in this large series, the patient survived for one year in only three, and for three years in none. Nephrectomy was performed by the lumbar route in 940 cases, the operation mortality being 4%. The transperitoneal route was used for more advanced tumours in 167 cases, with an operation mortality of 5%. After operation the survival rate for one year was 80%, for three years 44%, for five years 30%; after ten years only 17% remained alive. An interesting feature in this study of renal adenocarcinoma is the surprising improvement in the survival rate when post-operative irradiation was given; in the group of cases in which cure was expected, the survival rate for one year was 86%, for three years 53%, and for five years 49%; more remarkable still, 27% of the patients survived ten years, a distinct improvement on the rate after operation alone. The authors are not sure whether irradiation is of real value in prolonging survival when used as a palliative in inoperable cases.

The next group for study was that of transitional-cell carcinoma of the pelvis. It is notorious that for this condition the whole ureter must be removed as well as the kidney, either at the same time or soon after; otherwise recurrences are frequent. These tumours are very malignant as judged by survival rate, and the squamous-cell carcinoma of the pelvis is even more dangerous. Nephrectomy and nephro-ureterectomy were performed in 79 cases of transitional-cell carcinoma in which, at the time of operation, there was no involvement of the ureter or bladder. The survival rate for one year was 62%. The fall in the survival rate was gradual, and even after ten years it was still 41%. Squamous-cell carcinoma of the pelvis is a much rarer growth, often associated with stone, and usually caused by some chronic irritation, inflammatory or traumatic. After nephrectomy in a group of 48 cases, only about one-third of the patients survived for one year; of the remaining 30, only four were alive at the end of three years, and there were no five-year survivors. Simple papillary tumour of the pelvis was reported in 74 cases. Nephro-ureterectomy is necessary in such cases. The survival rate was good, being 95% at the end of one year, 87% after three years, and 50% after ten years. The most important primary tumour of the ureter is the transitional-cell carcinoma; only 15 of these were reported, 10 being treated by nephro-ureterectomy. Of the 15 patients, eight died within one year, and only two were alive at the end of four years.

[1] *British Journal of Urology*, December, 1951.

Of a series of 189 cases of Wilms tumour, a complete statistical survey was carried out in 138. The 138 patients in this group were treated by surgery and radiotherapy. In the easier cases (21) nephrectomy alone was performed; about half the patients survived for one year, and a third of them up to five years. In the group in which pre-operative irradiation was followed by nephrectomy, two out of thirteen survived for one year, and these two patients were still alive at the end of three years. A larger group (25) underwent nephrectomy and post-operative irradiation; one-third of the patients survived for one year, and one-quarter for three years. The general conclusion reached about the Wilms tumour group is that radiotherapy has no place as the sole form of treatment, but that in conjunction with surgery it is invaluable.

There is much more of interest in this paper, including a careful discussion of the pathology of the tumours with special reference to the prognostic significance of pathological features and to the distribution of secondary deposits. It is sufficient here to mention the conclusion that the most important prognostic factor is the histological grading of the tumour; with adenocarcinoma, invasion of the renal vein is more probable if the growth is of a high degree of malignancy, and with transitional-cell tumours of the renal pelvis the survival depends to a large extent on the histological degree of malignancy. The paper will repay the study of those interested. Details of the clinical material are set out and analysed in 40 tables and 65 illustrations, which include many photomicrographs.

THORACIC AORTOGRAPHY.

AUSTRALIAN radiologists and physicians returning from Sweden speak enthusiastically of the techniques used by workers in that country for visualization of the heart and great vessels. Descriptions of the methods used for ordinary angiocardiography have been published previously, and in his monograph, "Thoracic Aortography", now published as a supplement to *Acta radiologica*,[1] Gunnar Jonsson describes the technique used for visualization of the aorta with special reference to its value in patent *ductus arteriosus* and coarctation of the aorta. Classical venous angiocardiography, as introduced by Castellanos in Cuba and Robb and Steinberg in the United States, has not been entirely satisfactory in demonstrating lesions of the aorta though none can deny its value. The development of the surgery of coarctation of the aorta has led to more direct methods of visualization of the coarctation, and the method described by Jonsson leaves little to be desired. The technique is based on that of Radner, who injected dye into a catheter inserted via the right radial artery so that the tip lies in the ascending aorta. Jonsson and his co-workers inject the dye from a syringe driven by a simple but powerful mechanical device. The risks are easily avoidable and there have been no deaths.

In cases of patent *ductus arteriosus* the passage of dye from aorta to pulmonary artery gives positive proof of the presence of this anomaly, but most Australian clinicians would agree with Jonsson that the procedure is unnecessary in the usual case of patent *ductus arteriosus*. When the signs are atypical, as is usually the case when severe pulmonary hypertension coexists, aortography may provide valuable information, but one could hardly say that aortography is essential. Cardiac catheterization will provide similar information and in addition will demonstrate other associated abnormalities in the right side of the heart which aortography will not reveal. In cases of coarctation of the aorta, aortography is apparently carried out routinely in Stockholm before surgical resection and there can be little doubt of its value. The reproductions of the original films speak for themselves, and one must agree that the results are consistently better with thoracic aortography than with classical angiocardiography. Nevertheless, it is possible to resect coarctation of the aorta successfully without this new aid, as results from America, England and Australia have shown. This short monograph tells its story largely through its illustrations, which give convincing proof of the excellence of the Swedish techniques. It should prove stimulating to those interested in congenital heart disease.

[1] *Acta radiologica*, 1951, Supplement 89.

A STUDY OF ANÆSTHETIC FATALITIES.

IN 1935 the honorary medical staff of the Royal Adelaide Hospital appointed a subcommittee to investigate the problem of death during anæsthesia. The subcommittee was composed of a surgeon, a physician, a pathologist, a physiologist and an anæsthetist. Between July 1, 1936, and June 30, 1950, a total of 166,397 administrations of anæsthetics was reviewed. Associated with these were 142 fatalities, of which nine were due to causes other than anæsthesia, and 133 were related in greater or less degree to anæsthesia. These 133 fatalities have been reviewed exhaustively by Gilbert Brown, honorary consulting anæsthetist to the Royal Adelaide Hospital, in a paper which warrants the attention, not only of those who give anæsthetics, but also of surgeons and hospital administrators.[1] The paper is in two parts, the second part being devoted to the detailed statistical evidence on which the review is based. We are concerned here with the first part of the paper, in which Brown draws some important clinical lessons from the whole series of fatalities. The overall mortality rate was 0·8 per 1000 administrations, which, as Brown points out, is not unreasonable when compared with the figures of other institutions. Of the 133 fatalities, 7·5% were considered to be definitely preventible, and 18·1% probably preventible. In 27·8% of cases, it is possible that under other conditions of anæsthesia or of surgery a fatal issue might have been averted, and in 34·6% the patient's condition was such as to render his death more or less unavoidable. Several fatalities are regarded as being due to deficient pre-operative care of the patient, such as excessive premedication, lack of adequate replacement therapy, or faulty judgement in deciding upon the time and scope of the operation. Many deaths are attributed to faulty choice of anæsthetic agent or technique; the main faults listed are provision of atmospheres deficient in oxygen, neglect to secure patency of the air passages or adequate tidal exchange, misuse of the potent intravenous anæsthetics, failure to make adequate replacement of lost blood, and imperfect recognition of the danger of vomiting in cases of intestinal obstruction. Brown calls the attention of surgeons to the advantages of local analgesia in cases of "desperate risk" and to the embarrassment which use of the electrocautery can cause to the anæsthetist. He deprecates the tendency in modern anæsthesia towards "polypharmacy", especially when the anæsthetist is new to his work, and gives as an example the patient, aged seventy-nine years, who, in the course of a formidable operation for malignant disease of the tongue and jaw, received "Decicaine" as a local anæsthetic in the throat, thiopentone, nitrous oxide and oxygen with trichlorethylene supplement, and supplementary doses of thiopentone. It is scarcely remarkable that fatal cardiac failure ensued an hour after operation. Faulty anæsthetic technique is blamed for many fatalities, and Brown lists certain main faults: failure to protect the bronchial tree adequately against the entry of foreign matter; failure to maintain patency of the air passages or to clear them when obstructed; neglect to give manual "aid" to respiration in patients in an unfavourable posture; embarrassment of the patient's circulation by abrupt changes in posture; failure to treat convulsions (especially those due to poisoning by local analgesics) with intravenously given barbiturates and oxygen; misuse of carbon dioxide as a stimulant to depressed respiration. What Brown describes as a lamentable number of fatalities were attributed to inadequate post-operative care. The main faults were failure to prevent falling back of the tongue or

[1] *Royal Adelaide Hospital Reports*, November 30, 1950.

aspiration of blood or vomitus, misuse of morphine in the control of restlessness in hypoxic subjects, and failure to recognize the onset of pulmonary atelectasis and to give it sufficiently active treatment. Brown considers that all these facts are a good argument for the establishment in every hospital of a post-anæsthetic recovery room, duly equipped and staffed by trained personnel. He states that many cases in the series suggested the need for closer observation of the patient by the anæsthetist and for the keeping of an operation chart. Much valuable time was wasted in the giving of ineffective analeptics, subcutaneously, intravenously or into the myocardium. The time, it is suggested, would have been much more usefully employed in clearing the airways, initiating artificial respiration with oxygen, and performing cardiac massage. The value of pre-operative replacement therapy and of the blood bank was abundantly demonstrated, but in some cases replacement was excessive and led to the development of pulmonary œdema.

One of the most interesting of the points which emerge from this inquiry is the conception of a trained anæsthetist. He is described as a person well informed in general medicine and surgery, and therefore capable of bringing his patient into optimal condition for operation. He must be able to think along sound physiological lines, especially in regard to such matters as replacement therapy, transfusion and oxygen therapy. He must be a capable technician with a reasonable degree of mechanical sense. He must be conscious at all times of the problems of adequate pulmonary ventilation, and must be alert to recognize and treat the many complications of anæsthesia, not least of which is post-operative atelectasis of the lung. In conclusion, Brown makes the point that the creation of a standing committee upon anæsthetic fatalities will have a beneficial influence upon surgeons and anæsthetists alike. Such a committee does not exist to assign praise or blame. Its sole concern is the elucidation of facts about any fatality, so that its repetition may be avoided. For this elucidation, two essential requirements are laid down. The first is a self-analytical and absolutely candid attitude on the part of those who give evidence to the committee. The second is an accurate pathological report. This point warrants the most careful general attention, based as it is upon such a thorough investigation and such extensive experience.

INTRAVENOUS USE OF FAT FOR PARENTERAL FEEDING.

A MAJOR PROBLEM in parenteral feeding is associated with the need for a non-sclerosing preparation for intravenous feeding which contains a large supply of Calories in a small volume of fluid. Fat emulsions appear to offer a solution for this problem. Fat particles do not exert an osmotic effect, unlike dextrose and amino acids, and they are not excreted in the urine in significant amounts. Although the use of fat emulsions for this purpose is not new, difficulties in the preparation, storage and transport of suitable fat emulsions have prevented unrestricted use of the material. F. J. Stare and his associates have been investigating the production and use of fat emulsions for parenteral feeding of animals for some years. They have developed a stable fat emulsion which can be autoclaved under nitrogen gas and rarely gives any reaction when injected. It is made with coconut oil with specially purified soya bean phosphatide homogenized under pressure and under nitrogen. To the emulsion is added a 5% solution of glucose. The particles of fat are less than 1μ in diameter so that fat emboli are very unlikely to form. T. W. van Itallie, W. R. Waddell, R. P. Geyer and F. Stare have studied the use of this emulsion injected intravenously in human patients.[1] The injections were given to 35 patients with a variety of disorders. None of the patients showed pyrogenic or other untoward responses. Fifteen of the patients received 5 to 36 separate injections; each of them had at least 500 millilitres and several received as much as 2000 millilitres at one time. The preparations contained fat in concentrations of 10%, 12·5% and 15%, providing respectively 1100, 1325 and 1600 Calories per litre.

The role of fat given intravenously in parenteral nutrition is to provide Calories. By means of glucose and protein hydrolysates, given by vein, it is possible to realize the body's needs for carbohydrate and protein. However, it has never been practicable to meet energy requirements solely by parenteral feeding. An inadequate Calorie intake for a short time is not necessarily harmful to the patient who is acutely ill. However, during long periods of energy deficit, body protein is broken down to supply Calories and essential carbohydrates. Calories from fat stores are generally by no means adequate to supplement those from glucose and amino acids given parenterally. One patient suffering from peritonitis and persistent complete intestinal obstruction which prevented any oral intake was fed entirely by vein. For thirty-one days alcohol, glucose and protein hydrolysate were administered in liberal amounts, but the patient became increasingly cachectic. For the next thirty-six days, in addition to the conventional nutrients, he was given 36 injections of fat emulsion which provided a total of 42,214 Calories. The patient began to retain small amounts of food by mouth and the parenteral feeding was stopped. Ten days later the patient was convalescing satisfactorily. A litre of fat emulsion providing 1600 Calories can be given in one hundred and twenty minutes or less. Clearance of fat from the blood-stream is complete after four or five hours. No evidence of damage to the liver or of disturbance of the integrity of the red cell membrane has been found, nor has any patient shown clinical evidence of ketosis during or subsequent to the intravenous injections of fat emulsion.

[1] *A.M.A. Archives of Internal Medicine*, March, 1952.

"N.S.C.R."

ONE of the "alphabetical" bodies of Great Britain, little known in this country, is the N.S.C.R.—the National Society for Cancer Relief. It is a voluntary charity registered under the *Friendly Society Acts*. The objects of the Society are commendable: (*a*) to promote such conditions of living as shall secure the ultimate prevention of malignant disease; (*b*) to assist, advise and provide for sufferers from such diseases who are in need of present relief. By the dissemination of accurate knowledge it seeks to remove anxiety and fear. For sufferers who are in need it tries to provide special nourishment, bedding, clothing and warmth. It seeks to provide attention for necessitous cancer patients who are discharged from hospital and need domestic assistance and skilled home nursing. In certain circumstances it tries to arrange for holidays at convalescent homes and pays expenses. The work of the Society has grown. In 1931 it gave financial assistance to eight patients to the extent of £80. Last year it distributed £24,000 among 2100 sufferers. It has recently published a brochure entitled "The Book of Cancer Relief",[1] which presents "an outline of the position regarding cancerous diseases in Britain, and of the forces engaged in combating the scourge". It is full of useful information, but a great deal of it will be of use only in Great Britain, particularly that part dealing with regional hospital organization. The volume is commended to all persons in Australia who seek to do something to relieve the distress among sufferers from malignant disease in this country.

[1] "The Book of Cancer Relief: Presenting an Outline of the Position Regarding Cancerous Diseases in Britain, and of the Forces Engaged in Combating the Scourge", with a foreword by the Countess Mountbatten of Burma, C.I., G.B.E., D.C.V.O. London: Katherine Evans. 10" × 7½", pp. 92, with a few illustrations. Price: 2s. 6d.

Abstracts from Medical Literature.

DERMATOLOGY.

Fixed Drug Eruption from Aureomycin.

A. L. WELSH AND L. C. GOLDBERG (*A.M.A. Archives of Dermatology and Syphilology*, September, 1951) state that they were unable to find any reference in the literature to a fixed type of eruption from any of the antibiotics. They report the case histories of two patients in detail. The first case appears to represent a classic fixed type of drug eruption produced by aureomycin. In the second case, a fixed type of eruption from aureomycin appears to have developed in pigmented areas, the pigment representing a residual in the skin from a former eruption in the skin due to an entirely unrelated cause. Both patients had sensitivity to sulphonamides.

"Banthine."

C. S. BROWN AND I. L. SANDLER (*Archives of Dermatology and Syphilology*, October, 1951) state that Gumson and his co-workers have recently advocated in a preliminary report of four cases the successful use of the anticholinergic drug "Banthine Bromide" (β-diethylaminoethyl xanthane-9-carboxylate methobromide) in the treatment of hyperidroses. The purpose of the authors' report is to describe the use of "Banthine Bromide", not only in the treatment of hyperidrosis, but also in the treatment of several of the common dermatoses aggravated or possibly produced by excessive sweating. The first group of patients were those with functional disturbances of the sympathetic nervous system, characterized by localized hyperidrosis, involving palms, soles and axillæ alone or conjointly. The second and larger group of patients were those with several common dermatoses, such as contact dermatitis of the hands, vesicular eruptions of the hands and feet (dyshidroses), or intertrigo. Varying degrees of excessive sweating accompanied each of the conditions. Patients with erythematous vesiculo-papular contact dermatitis were chosen because the irritating properties of palmar sweat frequently prolong the period of recovery. Patients with recurrent pruritic deeply situated vesicles of the hands and feet, but with no evidence of fungous infection, were also given "Banthine Bromide". These vesicles were typical of dyshidrosis, which is a persistent disease accompanied by hyperidrosis and believed to be a psychosomatic dermatosis. Patients with intertrigo were also selected because friction and external irritants stimulate the regional sweat glands. The increased production of sweat macerates the skin and an exudative type of dermatitis follows. The authors found that excessive sweating in patients with uncomplicated hyperidroses can be effectively controlled with "Banthine Bromide". Patients with contact dermatitis associated with excessive sweating responded more quickly to the combined use of local applications and "Banthine" given orally. Although the exact ætiological factors of the various vesicular eruptions of the hands, fingers and feet are controversial, the authors observed a more rapid involution of vesicles when "Banthine" therapy was used. The drug is also useful in *hydradenitis axillaris suppurativa*, the sweating of the menopause, and nocturnal sweating. The dose administered was 25 milligrammes of "Banthine Bromide" three times a day, and this was increased to 50 milligrammes if necessary. Each week the daily dosage was increased 100 milligrammes until the desired clinical results were obtained. The maximum daily dose given to two patients was 400 milligrammes.

Clinical Studies in Percutaneous Absorption.

M. V. NADKARNI, D. B. MEYAR, R. C. CARNEY AND L. C. ZOPF (*Archives of Dermatology and Syphilology*, September, 1951) state that there is a trend for dermatologists to prescribe washable ointment bases for medications employed in topical therapy. The recognition of the fact that there is considerably increased absorption from such bases in comparison with the absorption from the traditional oleaginous bases has led to the present investigation, which is concerned with the quantitative evaluation of the comparative increase of absorption. On the normal skin the use of a water-soluble vehicle promotes greater absorption of an insoluble dye (phenolsulphonphthalein) incorporated therein than does the use of an oleaginous base. The water-soluble base used was a mixture of equal parts of polyethylene glycol 4000 and polyethylene glycol 400. White petrolatum U.S.P. was used as the oleaginous base for comparative study. Phenol sulphonphthalein was selected as the tracer material because of the accuracy with which amounts of it can be quantitatively determined in urine by standard photoelectric procedures. There is a pronounced and significant increase in absorption of the insoluble tracer dye phenolsulphonphthalein through inflamed skin, most pronounced with eczematous dermatitis and much greater with polyethylene glycol as the vehicle than with white petrolatum. This increase may range to as high as 12 times greater absorption from water-soluble base on eczematous skin than from oleaginous vehicle on normal skin and suggests the possibility of the absorption of toxic amounts of certain drugs, even those relatively insoluble, if they are incorporated in washable vehicles in the concentration generally used in oleaginous ointments. This observation indicates the necessity for reducing the concentration of the therapeutic agents.

Adult Form of Chronic Porphyria with Cutaneous Manifestations.

L. A. BRUNSTING AND R. A. ALDRICH (*The Journal of the American Medical Association*, July 28, 1951) discuss a form of chronic porphyria in which the disease appears first in adult life with cutaneous signs, such as a blistering and erosive tendency of the skin, especially on the dorsum of the hands, on exposure to the sun and with trauma, as well as with a change in the complexion of the face and adjacent areas to a ruddy or violaceous hue. Associated symptoms of abdominal colic or nervous disorder occasionally occur. There may be spotted or diffuse melanosis of the exposed skin and the hair and occasionally hypertrichosis. Milia are seen in the healed scars of the denuded and infected lesions on the hands. The authors state that a survey of the records in the 17 cases reported indicated that some damaging influence on the liver was chiefly responsible for the development of clinical symptoms. Alcohol was the main offender. Active *diabetes mellitus* occurred in three cases and syphilis in two. In two cases there was a history of the use of barbiturates. With appropriate management the course of the disease was relatively benign. The results of quantitative analysis of urinary porphyrins in the 17 cases are presented. The urine may be dark amber, sometimes pink and rarely red. In certain stages of the disease the urine may contain few or no abnormal porphyrins. Sometimes porphobilinogen is present. The disease is commoner than is generally supposed. In the light of present knowledge, the exact classification of this type of porphyria is unsettled.

Acne Necrotica.

C. STRITZLER, R. FRIEDMAN AND A. B. LOVEMAN (*A.M.A. Archives of Dermatology and Syphilology*, October, 1951) state that Sabouraud first described *acne necrotica miliaris* as an abortive form of *acne necrotica* (*acne varioliformis*) and the pathological picture as that of *acne necrotica*. They report a case notable because of severity and extensive involvement and because it demonstrates a probable relation between *acne necrotica miliaris* and *acne necrotica*. Prolonged remission was induced by parenterally administered penicillin after numerous therapeutic agents had failed. Absence of seborrhœa, intense itching, pinhead-sized crusts and vesicles over the scalp and a tendency to relapse all speak in favour of *acne necrotica miliaris*. A tendency for papules to develop necrotic centres and to leave varioliform scars speaks in favour of *acne necrotica*. The authors consider *acne necrotica miliaris* an early, abortive form of *acne necrotica*. They state that *acne necrotica* responds to adequate doses of penicillin administered parenterally, but it must be continued for an indefinite period, since flare-ups occur promptly when it is discontinued. *Acne necrotica* also responds to sulphapyridine and streptomycin therapy.

Green Nails.

M. MOORE AND M. D. MARCUS (*A.M.A. Archives of Dermatology and Syphilology*, October, 1951) state that green nails are not uncommonly encountered in the routine examination in onychomycosis. Usually they are the result of an infection with various species of Aspergillus. These nails have been described as being of a light to dull green colour with a deep-seated discoloration of the nail plate. Not all green nails are due to aspergillosis. One of the authors has observed several nail infections which were due to *Candida albicans* and in which no other organism could be implicated by direct examination of the infected material or by culture. The infected nails in these cases were light to dull green; the lesion began at the outer margin of the nail and extended into the nail plate. The observation of onychomycosis caused by both a yeast-like organism, *Candida tropicalis*, and *Pseudomonas æruginosa* (*Bacillus pyocyanea*) throws more light on the ætiology of green nails. Of causes of

onychomycoses, aspergilli are perhaps the best known as producers of green nails. Over a period of years it has been observed that in some cases of onychomycosis a dull green colour is seen. These cases have been found to be due to *Candida albicans*. Green nails may be caused by dyes, chemicals other than dyes, various species of Aspergillus, strains of *Candida* (*Syringospora monilia*) *albicans*, and involvement with *Pseudomonas æruginosa* (*Bacillus pyocyanea*).

UROLOGY.

Mortality of Perurethral Prostatic Resection.

C. D. CREEVY (*The Journal of Urology*, May, 1951) states that free hæmoglobin formed in the bladder by contact between blood and the water used as the irrigating fluid during endoscopic resection may be drawn into the circulation if large prostatic veins are opened. When this free hæmoglobin reaches the kidneys, renal vasospasm results, which may cause severe or even fatal renal damage, particularly in the presence of rapid loss of blood, hypertension, bacteriæmia or pre-existing renal damage. This reaction can be prevented by the use of an isotonic irrigating solution (glucose, glycine or mannitol). The author now reports on 1000 consecutive cases of resection in which glucose or glycine was the irrigating solution, and finds that the surgical mortality is only 0·6%. The mortality of perurethral resection is therefore far below that yet reported for any of the open methods of enucleation of a prostatic adenoma.

Treatment of Wilms's Tumour.

C. RUSCHE (*The Journal of Urology*, June, 1951) publishes statistical data pertaining to 40 patients with Wilms's tumour, ranging in age from three months to ten years, with one case of bilateral involvement. He also reports a case of the development of a Wilms's tumour on the same side, four and a half years after removal of an adrenal cortex tumour. No standard treatment was used in this series. Five patients, who are alive at ten years of age, had radiation treatment as an adjunct to nephrectomy. Of these, three received it pre-operatively and one post-operatively, while the other child, who is still alive just on five years after operation, had radiotherapy both before and after nephrectomy. The author states that the results of this study suggest that radiation therapy should be instituted as soon as the diagnosis is made, and that nephrectomy should be postponed until after such treatment.

Pathology and Prognosis in Renal Tumours.

N. C. FOOT, G. A. HUMPHREYS AND W. F. WHITMORE (*The Journal of Urology*, August, 1951) have made a study of the pathology and prognosis of renal tumours encountered at two large New York hospitals over about fifteen years. Of 706 cases designated as renal tumours, 411 were eliminated from the study as being without any pathological confirmation. This left 259 for study. As for incidence, the group of "renal cell" carcinomata was the largest (107), while next in order were the transitional cell carcinomata from the conducting epithelium (43). Wilms's tumours accounted for 31 cases, while purely epithelial embryonal cases numbered 16. Of the patients suffering from definite renal-celled carcinoma 38% were alive five years after nephrectomy. Of 19 patients with definite transitional-celled carcinoma, only one was alive five years after nephrectomy, and he died of carcinoma in the seventh year. Of 20 with definite embryonal carcinoma only one was alive five years after nephrectomy. The tumours in the two latter groups are, therefore, highly malignant. To determine the prognosis better in the large and important group of renal-celled carcinomata, variations in the histopathology were studied. The best prognosis was offered by those renal-celled tumours with clear, regular cells having isometric nuclei arranged in cords and strands with thick, dense septa. The worst prognosis was offered by those with irregular, granular cells having anisometric nuclei, the cells being arranged in tubules and papillæ, with irregular, thin septa.

Surgery of Hydronephrosis.

R. R. BERNEIKE AND C. L. DEMING (*The Journal of Urology*, July, 1951) state that many diverse operations for the relief of hydronephrosis are being advocated from various parts of the world; this would tend to suggest that no one procedure has been widely accepted by urologists of today for the conservative treatment of this rather common disability. The authors describe an operation which has given good and lasting relief in 27 cases out of 30 attempts. The method is applicable to all obstructions at the ureteropelvic junction, to abnormal and high implantations of the ureter into the renal pelvis, and finally to strictures of the upper portion of the ureter. Practically all of the extra-renal bulging of the distended pelvis is cut away and discarded. This is facilitated by placing a fine silk traction suture on the upper and lower part of the pelvis just near the upper and lower limits of the renal hilum. The anterior and posterior cut edges of the pelvis are then sutured with the very finest chromicized catgut, the mucosa being inverted and the lowermost one centimetre being left unsutured. This gap is left for the subsequent anastomosis of the ureter to the pelvis. The pelvic suture line is reinforced by interrupted sutures in the fascia which covers the renal pelvis. Again fine chromicized gut is used. Previously the ureter has been cut across just below its lowest narrow point, and now a vertical incision is made in its lateral aspect, about three centimetres below its upper cut-off end; this is for insertion of the "Latex" "T"-tube which will be used for both splinting and drainage of the urine. The tube varies in size from 14F in the child to 18F in the adult. The upper arm of the "T"-tube passes up into the renal pelvis, while the lower and shorter arm passes a little way (two centimetres) down the ureter. The long draining or "vertical" limb of the "T" passes out to the loin just below the lower pole of the kidney, to which it is attached by an anchor suture of plain catgut. This keeps the whole "T"-tube steady. The "T"-tube is further anchored by silk to the skin about the middle of the lumbar incision. The tube is removed on the seventeenth day. The limitations of this operation are in general those which contra-indicate renal plastic surgery. The presence of well-developed compensatory hypertrophy in the opposite kidney probably precludes satisfactory restoration of function in the operated kidney. The presence of long-standing pyelonephritis on the obstructed side seems to jeopardize the result.

Osteitis Pubis.

H. MORTENSEN (*The Journal of Urology*, September, 1951) has made a study of the extremely painful disease known as *osteitis pubis* on the basis of the replies to a *questionnaire* sent by him to urologists in Australia and New Zealand. Forty-four cases were collected from the practices of 16 out of 37 urologists who answered the *questionnaire*. Of these, seven occurred in the author's own practice. He states that pain is the outstanding feature, coming on two to four weeks after operation, but this may be delayed even more. Any muscles attached to the anterior bone of the pelvic girdle cause the most extreme pain when they pull on the affected bone, hence the patient lies rigid and in acute fear of any movement. The great majority of cases in recent years have occurred after the operation of retropubic prostatectomy, introduced a few years ago by Millin, but it also occurs after other operations on the bladder and urethra. Kirz in 1947 described three factors which may be responsible: (i) deliberate opening of the pre-vesical space; (ii) avulsion of the fibres of the rectus muscle or of the two layers of the transversalis fascia attached to the pubic bone; (iii) rupture of the pubo-prostatic ligaments in the process of enucleating the prostate. No treatment seems to be of any avail, but the disease is self-limited and disappears after a few or many months.

Elliptical End-to-Side Uretero-Pelvic Anastomosis.

W. W. MILLER (*The Journal of Urology*, September, 1951) reports on three cases of hydronephrosis with stricture and faulty implantation at the uretero-pelvic junction. He has tried in these cases the principle recently advanced by Reed Nesbit for ureterointestinal anastomosis, by direct end-to-side elliptical junction. The narrowed ureter is severed at its constricted junction with the renal pelvis. It is then split longitudinally on its anterior surface for about 1·5 centimetres, or until the strictured area has been passed. A similar incision is made through the adjacent wall of the renal pelvis, descending from the severed point. A roughly elliptical opening now obtains in both pelvis and end of ureter, and these are anastomosed with very fine chromicized gut (00000) on an atraumatic needle, the continuous principle being used. A nephrostomy drain and ureteric splinting catheter are used. The kidney should be fixed in good position by simple nephropexy. The splint is removed in three weeks, and a descending pyelo-ureterogram made through the nephrostomy tube. If this is satisfactory, the nephrostomy tube is clamped and left in place for three more days, at the end of which time an excretion urogram should show satisfactory function of the kidney after thirty minutes; then the tube can be removed and prompt healing of the wound be expected.

Special Articles for the Clinician.

(CONTRIBUTED BY REQUEST.)

XXVI.

CHOICE OF ANTIBIOTICS.

THE purpose of this article is to clarify the therapeutic use of antibiotics, giving a survey of the value, defects and dangers of those available in clinical practice. Many readers by their own experience will already have a satisfactory scheme for treatment of the common infections, and although the following facts are not new they may be reassuring.

For the correct management of infections, a clinical diagnosis having been made, it is necessary to think in terms of bacteriology and, when possible, to obtain laboratory help in isolation and identification of the organism, as well as determining its sensitivity to the drugs. In heavy infections (indicated usually in a clinical way by severe disease), a combination of two or even three agents may be effective. Generally, in acute infections, it is best to use one drug in adequate dosage rather than a number given in a "shot-gun" method.

Sensitivity tests are of considerable value, but can be misleading—for example, sensitivity tests in cases of typhoid may show the organism equally sensitive to aureomycin and "Chloromycetin", but "Chloromycetin" is the better drug to use.

Though a patient may become sensitive to penicillin and further administration produce urticaria and exfoliative dermatitis, sensitivity to other antibiotics is very rare.

It is also necessary to assure patients that "they do not get used to a drug" and that repeated use, for example, of penicillin for frequent streptococcal infections will not prevent them adequately combating a future infection. Organisms admittedly become resistant to antibiotics, and this happens chiefly in two ways. First, the appearance of a resistant strain in clinical infections due to a particular organism which was originally sensitive is due to the fact that a few resistant organisms were present at the beginning, but very much in the minority, and appeared in abundance only on the destruction of the sensitive organism. An example of this is in *Hæmophilus influenzæ* meningitis. Second, under the influence of the antibiotic the organism may develop mutants which are resistant to that antibiotic.

If it is likely that a patient will benefit by the use of an antibiotic, and there is reasonable certainty that the organism is sensitive, the antibiotic should not be withheld because of the danger of the development of resistant strains of the organism.

Penicillin-resistant staphylococci are of special interest, in that their resistance is due to the production of penicillinase, and practically no amount of penicillin can influence such organisms. Fortunately, these organisms are usually sensitive to other antibiotics.

Dosage.

Before the individual antibiotics are discussed, a general statement on dosage is important. There is a limit to the effective dose, and increasing the dose above that will not be of value. It varies with different organisms. Penicillin has been used in a dose of 2,000,000 units given three-hourly by the intramuscular route, but the upper limit is probably 1,000,000. The limit with aureomycin is probably 70 to 80 milligrammes per kilogram per day. Any amount in excess of that is destroyed and does not influence the organism.

Periodicity of Dosage.

When given by mouth the group of antibiotics, chloramphenicol, aureomycin and terramycin, are best given four-hourly or six-hourly. There is considerable controversy concerning the best intervals for penicillin; the original advice of Florey of three-hourly injections has much to commend it for severe infections. Whatever the dosage and method of administration, the important thing is the time the antibiotic is at an effective level in contact with the organism. Some authorities regard twelve-hourly injections as ideal with any infection in which penicillin is used. With subacute and chronic infections, the time interval between injections may be lengthened, in the case of penicillin by the use of procaine penicillin, while streptomycin is effective in cases of tuberculosis when given at intervals up to forty-eight hours between injections.

Prophylactic Use of Antibiotics.

It is an accepted principle, and one to be encouraged, that infections can often be prevented by the use of the correct drug in the right dosage. This fact is well known by surgeons and applied in abdominal, orthopædic and reparative surgery. Adequate prophylactic therapy can well be used for teeth extractions. For patients with certain heart lesions, to prevent endocarditis following tonsillectomy and teeth extractions, a prophylactic antibiotic should be available. Consideration can be given to similar usage in routine tonsillectomy.

Toxic Effects of Antibiotics.

The development by a patient of allergic sensitivity to penicillin has been mentioned, and the misery of the prolonged skin irritation, urticaria and joint swellings must, if possible, be avoided. It is rare in children.

Other toxic features associated with penicillin, chloramphenicol, aureomycin and terramycin given orally are nausea, vomiting and sore mouths. Looseness of the bowels and watery diarrhœa with excoriation of the buttocks are not uncommon with chloramphenicol, aureomycin and terramycin.

Monilia infection in the mouth, around the anus and elsewhere is a reported complication of antibiotic treatment. Though yeast organisms may readily multiply in the mouth and around the anus when bacteria are inhibited by antibiotics in chronic chest infections, dangerous complications of this nature are rare.

Streptomycin and dihydrostreptomycin can cause vestibular disturbances if treatment is prolonged.

For many reasons, including the cost of antibiotics, the danger of development of resistant strains of organisms, sensitivity of the patient and monilia infection, the indiscriminate use of antibiotics is to be deprecated. Further, they should not be used for a period longer than is necessary.

In the choice of an antibiotic, the above points will influence the selection. An additional factor of importance is whether or not a particular drug or preparation is available free to the patient through the Pharmaceutical Benefits Regulations.

Penicillin.

Penicillin can be administered by injection or orally.

Oral Administration.

Oral administration is quite practical, both in adults and in children. A dose at least four times that used for a similar infection treated by injection is advised. Penicillin is available commercially in tablet form and in sweetened syrup. It can be made up immediately before use in liquid form from the crystalline dried powder and sweetened if necessary. After preliminary injections in the severe early acute phase of an illness, oral administration can follow.

Administration by Injection.

For small infants weighing under 40 pounds, the dosage of crystalline penicillin is 5000 to 10,000 units per pound of body weight daily. Older children, weighing over 40 pounds, need 200,000 to 400,000 units daily. Adults require 300,000 to 1,000,000 units daily.

Procaine penicillin in aqueous suspension is useful and gives an effective blood level for eighteen hours. Procaine and crystalline penicillin can be combined. Procaine penicillin in arachis oil with aluminium monostearate added was useful for one dose daily therapy, but its stickiness and general difficulty of administration compared with the aqueous solutions has caused it to drop out of favour. An effective blood level can be obtained for thirty to forty hours. Many and varied are the schemes tried for the administration of penicillin, and it is important to reduce the number of injections as much as possible. The longer the drug is at an effective blood level the more useful it will be. This can be achieved by frequent intermittent dosage or use of a slowly absorbed product. It is best to give the drug three-hourly in severe infections, though Marshall (1951) believes that this view is open to question and advocates twelve-hourly dosage as the most suitable for crystalline aqueous penicillin. A good routine for debilitated newborn infants is 150,000 units of procaine penicillin given daily, or 50,000 units of crystalline penicillin given twelve-hourly by the subcutaneous route.

For intrathecal penicillin therapy the dose is 10,000 units of crystalline penicillin daily.

Penicillin Sensitivity.

As mentioned above, the development of severe urticaria with its irritation and misery, lasting seven to ten days and occurring five to ten days after the injection of penicillin, is rare in children but still quite commonly encountered in adults. For that reason it is best not to use penicillin by local application unless there is a strong indication to do so, and even injections are not to be considered lightly.

Streptomycin.

The place of streptomycin is particularly in the treatment of tuberculosis, of some penicillin-resistant staphylococcal infections and of other infections, including some due to *Bacterium coli*. Dihydrostreptomycin was at first thought to be equally as effective as streptomycin without its toxicity. It is now known that dihydrostreptomycin is just as toxic as streptomycin, and possibly more so.

TABLE I.

Present-Day Usage of Antibiotics in Infection.

Infection.	Penicillin.	Streptomycin.	Aureomycin.	Chloramphenicol.	Terramycin.
Streptococcal:					
β-hæmolytic	I	II	II	III	II
α-hæmolytic	I	II	II	..	II
Non-hæmolytic	I	..	II	..	II
All enterococci	II	..	I	..	II
Staphylococcal	I	..	I	II	III
Pneumococcal	I	III	II	II	II
Neisserian:					
Neisseria meningitidis ..	I	..	II	III	U
Neisseria gonorrhœæ ..	I	II	III	III	III
Diphtheritic ..	I (antitoxin)	..	..	..	U
Tuberculous ..	..	I (*plus* PAS)	..	..	..
Anthrax ..	I	..	I	..	U
Clostridial:					
Gas gangrene	I	..	U	U	U
Tetanus ..	?	..	..	..	..
Gram-negative bacillary:					
Bacterium coli	II	II	I	I	I
Proteus ..	..	I	..	..	II
Bacterium aerogenes ..	..	II	I	I	U
Pseudomonas æruginosa (pyocyanea)	..	II (Polymyxin is best)		..	II
Brucella ..		I	I		

I = first choice. II = second choice. III = third choice. .. = no value. U = unknown.

For acutely ill patients with miliary tuberculosis and for those with tuberculous meningitis, streptomycin is given six-hourly for the first two weeks. In these cases later in the disease, and in chronic cases, once-daily injections are used. An effective response can sometimes be obtained with an interval of forty-eight hours.

Dosage.

The usual dosage of streptomycin is 20 milligrammes per pound of body weight per day, but seldom more than a total of one gramme per day. A dosage of two grammes daily is used in the early stage of treatment of miliary tuberculosis. The daily intrathecal dose is 25 milligrammes for *Hæmophilus influenzæ* meningitis in an infant and 50 to 100 milligrammes for *Hæmophilus influenzæ* meningitis in children over five years, also for adults and for most patients under treatment for tuberculous meningitis.

Streptomycin and dihydrostreptomycin can be mixed with crystalline penicillin in the same syringe if both drugs are to be administered either intramuscularly or intrathecally.

Oral Administration of Streptomycin.

A dose of 100 to 200 milligrammes of streptomycin given three or four times daily by mouth has been of value in the treatment of Salmonella bowel infections, particularly those due to *Salmonella typhimurium*.

Chloramphenicol.

The valuable antibiotic "Chloromycetin", developed by Parke, Davis and Company, has been synthesized and given the name chloramphenicol. It is very effective against typhoid fever and scrub typhus. It has been used for a wide range of infections, including so-called primary atypical pneumonia and streptococcal, pneumococcal, *Hæmophilus influenzæ* and certain staphylococcal infections. Considerable publicity has been given to its apparent value in *Hæmophilus pertussis* infections (whooping cough), but these reports require further confirmation. In our experience the course of the disease was not shortened by "Chloromycetin" when given after the tenth day of symptoms.

In some cases of bowel infection the patients improved with "Chloromycetin". *Shigella flexneri* and other dysenteric organisms are found sensitive in a number of instances, but clinical response does not always follow its administration.

Among urinary tract infections, some due to *Bacterium coli* respond quite well, as they often do also to sulphonamides and alkalinization. *Proteus vulgaris* and *Pseudomonas pyocyanea* infections are not consistently cleared.

TABLE II.

Suggested Combinations of Antibiotics in Severe Infections.

Infection.	Penicillin.	Streptomycin.	Aureomycin.	Chloramphenicol.
Severe staphylococcal ..	I	..	I	..
Subacute bacterial endocarditis	I		I	
Acute bacterial endocarditis:				
α-hæmolytic streptococcus	I	..	I	..
Pneumococcus	I	..	I	..
Meningitis:				
Pneumococcus	I	..	I	..
Staphylococcus	I	..	I	..
Gram-negative coccus ..	..	I	I or	I

I = first choice. .. = no value.

A recent report indicates that chloramphenicol may be used locally as a 5% strength powder, or preferably as a solution in propylene glycol.

The oral dose of chloramphenicol is 20 to 40 milligrammes per pound daily given six-hourly. Initial administration of half the daily requirements in the first four hours is recommended for severe infections. These doses mean practically half to one capsule six-hourly for an infant under three years of age, one to two capsules six-hourly for a child aged four to ten years, and two to three capsules six-hourly for an adult.

Aureomycin.

The golden-coloured powder aureomycin is bitter to taste and it has been combined with flavouring in a sweetened powder, particularly for children.

Developed by Lederle's, it is a most effective drug against a wide range of organisms, being similar to "Chloromycetin" and terramycin.

Local custom has grown to use aureomycin for penicillin-resistant staphylococcal infections, and a good response is also found with other staphylococcal, pneumococcal, streptococcal and *Hæmophilus influenzæ* infections. It is reported to be of value against rickettsiæ in a similar way to "Chloromycetin".

Its true place is not yet clarified in urinary tract and bowel infections, and there are examples of aureomycin being quite effective in mastering infections with Gram-negative organisms.

In addition to the flavoured "Spersoid" preparation, there are capsules of 250 and 100 milligrammes, and a powder for making a solution and giving by intravenous injection.

Local eye application is also possible. The dose is similar to that of "Chloromycetin", but we are informed by the manufacturers that a smaller dose may be used than was previously recommended—for example, 250 milligrammes six-hourly for an adult. Before this dosage scale is adopted, further investigation is needed.

Terramycin.

Though it is available through the Pharmaceutical Benefits Regulations only for urinary tract infections which have not responded to other treatment, terramycin has a wide range of activity similar to that of aureomycin, and success has been obtained in the treatment of streptococcal tonsillitis and pneumococcal pneumonia. It is just as effective as "Chloromycetin" in the management of whooping cough.

It is available in capsules of 100 and 250 milligrammes, as a powder to be made up in a sweet syrup, and for local eye application and intravenous administration.

The oral dose is similar to that of "Chloromycetin".

Conclusion.

Tables I and II, slightly modified from those originally presented by Perrin Long, have been found to be a good practical guide.

There are still a number of organisms which do not regularly respond to antibiotic treatment, and these include *Proteus vulgaris* and *Pseudomonas æruginosa (pyocyanea)* infections. Brucella infections incline to recur in spite of newer methods of treatment. The less known antibiotics, neomycin and polymyxin B, are still regarded as too toxic for general use. Polymyxin E has been used for the treatment of meningitis due to *Hæmophilus influenzæ*. Bacitracin may have a place in the local treatment of wounds.

STANLEY WILLIAMS,
Melbourne.

Reference.

Marshall, E. K. (1951), "Schedules of Antibiotic Administration", *The Journal of the American Medical Association*, Volume CXLVI, page 1062.

British Medical Association News.

SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held on April 24, 1952, at the Robert H. Todd Assembly Hall, British Medical Association House, 135 Macquarie Street, Sydney, DR. R. H. MACDONALD, the President, in the chair.

Dangers of Antibiotics.

DR. F. H. HALES WILSON read a paper entitled "The Dangers of Antibiotics" (see page 869).

DR. E. F. THOMSON read a paper entitled "The Dangers of Antibiotics" (see page 870).

DR. V. M. COPPLESON, in opening the discussion from the surgical point of view, said that the problem had particularly interested him during the last two years. Much work had been done to determine what was the best form of antibiotic to use in surgery, and the conclusion reached was that the most suitable were penicillin and "Chloromycetin". Dr. Hales Wilson, in setting out the dangers, had rather lumped all the antibiotics together, and had referred to some of the reactions which followed one of them (streptomycin) as if they applied to them all; Dr. Wilson had, of course, not intended to do so, but his remarks had contained that suggestion. Untoward reactions differed with each of the antibiotics, and were related to dosage in some cases and to sensitivity. One of the most important problems arising in regard to antibiotic therapy was the question of the alteration of microbial flora by the development of resistant organisms or the substitution of fungous infections. Dr. Thomson had described a growing resistance to several antibiotics on the part of a number of organisms at the Royal Prince Alfred Hospital; the statement should have been accompanied by details of the dosage used at that hospital. Dr. Coppleson said that he understood that speaking generally the Royal Prince Alfred Hospital was a low-dosage hospital. He thought that results from hospitals where higher dosages were used might be quite different, as he believed that the development of resistance was largely due to exposure of the organisms to insufficient concentration of the antibiotic. Some time previously he had treated a patient suffering from a serious cellulitic infection of a wound. It was not influenced by streptomycin, by large doses of penicillin given parenterally or by "Chloromycetin" given orally. The wound was opened and "Chloromycetin" was applied locally. Within a few hours the patient's whole condition had changed; for that the application of the high concentration of the antibiotic was undoubtedly responsible. It was a striking observation. It was confirmed in a number of other cases, and the conclusion was reached that that antibiotic was much more effective by local application than when given by mouth. Dr. Coppleson said that it had been the subject of a paper by himself, which had been published in *The Lancet* (1951), Volume II, at page 65. A paper in *The Lancet* (1952), Volume I, page 541, by Sir Harold Gillies, Flint and Reid, of the Basingstroke Plastic Unit, had since confirmed the observation. They stated that they had obtained a rapid bacterial clearance of a wide variety of wounds infected with penicillin-resistant or insensitive organisms by local applications of "Chloromycetin". Dr. Coppleson said that his thesis was that the strength of the antibiotic brought into contact with the organism was an important consideration in the question of the development of resistance. An investigation of the matter had been begun in July, 1951, and been interrupted, to permit a more careful study of the material being used, and shortly a microcrystalline sterile powder specially prepared for local use would be available for further study. Dr. T. J. Claffey had been put in charge of an investigation of the effects of the local application of chloramphenicol to leg ulcers and its use in infected wounds. The first finding had been that when dilute solutions were used, resistant organisms were produced. Since greater strengths and pure powder had been used, resistance in organisms had been overcome. As a surgeon, he differed strongly from Dr. Thomson in regard to the use of chloramphenicol in surgery. Surely it was the ambition of all surgeons to have aseptic wounds, and their aim to conquer sepsis. Nowadays, whilst it was almost certain that first intention healing would occur in most wounds, there were other types of wounds in which one could not be so certain, or would want to ensure it—for example, when foreign bodies were inserted, in the presence of silk sutures or in skin grafting. By the use of pure chloramphenicol powder in skin grafting, it was possible to obtain almost 100% aseptic healing. Dr. Coppleson felt that the local application of antibiotics was destined to play a large part in everyday surgery and in bowel surgery, in which by their aid it was now possible to sterilize the contents of the bowel. Dr. Coppleson then referred to streptomycin. He thought that for the most part it had little place in surgery. He referred to a patient with tuberculosis of the testicle and prostate, in the care of Dr. Cotter Harvey and himself, who was treated with streptomycin and PAS with dramatic results. The antibiotics, and particularly penicillin in large doses and chloramphenicol applied locally, had, he believed, great future scope in surgical practice, but they needed to be used with judgement and with care.

DR. PHYLLIS ROUNTREE said that her first point concerned the emergence of antibiotic-resistant organisms in hospital environments. It might be asked why that phenomenon had not been observed in the community outside hospitals, among which penicillin in particular was probably used almost as freely as in hospitals. The figures for out-patients' strains of staphylococci were probably not a true measure of the incidence of resistant infections in the general population, since many of those people had lesions which entailed many visits to the out-patient department where opportunities for cross-infection existed. Cross-infection was the keyword. It was only in hospitals that opportunities for mass cross-infection existed. It was only there that large numbers of people were brought together in an environment saturated with a rich and varied resistant flora, and where the ministrations of the surgeons provided that flora with further suitable and accessible breeding grounds. For the purposes of the present discussion it mattered little whether the immediate source of the cross-infecting organisms was the ward atmosphere—for example, the air and bed-clothing—or the skin, clothing or noses of the nursing and medical staff. At the Royal Prince Alfred Hospital investigations had shown that new resistant strains appearing in patients as a result of antibiotic therapy were speedily established in the hospital environment and were readily passed to the noses of the staff and to the lesions of fresh patients. On the other hand, if an antibiotic-resistant strain arose in a patient treated in his own home, that would be a matter of concern to the patient and to his doctor; but the number of suitable recipients of the new strain would not be large, nor would conditions for its spread be likely to be present. From the ecological point of view that strain would have little opportunity of survival. It was necessary therefore to differentiate between the ecology of organisms in hospital environments and in the environments outside hospitals.

Dr. Rountree went on to say that her second point concerned the process by which the antibiotic-resistant strains appeared. Selection of strains which were naturally resistant had no doubt occurred in hospitals through the use of antibiotics, and that would affect the overall picture of the distribution of resistant and sensitive strains in a particular environment. In the disappearance of penicillin-sensitive strains of staphylococci from hospitals that process had undoubtedly been operating. However, it was necessary to distinguish between the overall effect of antibiotics on mixed populations of microorganisms and the effect of antibiotics on individual strains. Considerable argument still

raged as to whether the latter effect was due to adaptation or to mutation. Penicillin resistance in staphylococci isolated from patients was due to the ability to produce a penicillin-inactivating enzyme, penicillinase, and in only one case had that ability been shown to arise in the test tube, so that in the laboratory they could not carry out tests for the appearance of those mutants in cultures. However, streptomycin-resistant strains were similar whether arising *in vivo* or *in vitro*, and it had been shown in *Bacterium coli* and *Staphylococcus pyogenes* that those mutants arose in very small numbers in all cultures, whether the antibiotic was present or not. One in every 10,000,000,000 cells in a culture showed that mutation, which was then inherited by all the progeny of the mutated cell. At first sight that might seem such a low mutation rate that it was unlikely to have survival value for the strain producing it. However, when one considered the enormous numbers of bacteria that might grow in a suitable nutrient medium, such as urine, or in a large infected surgical wound or burn, it was easier to appreciate that such mutations could and did occur. There was evidence that such had been the origin of many of the strains now found in hospitals. Similarly it might be supposed that small dosages of antibiotics in concentrations that were inadequate to deal with large numbers of infecting organisms would allow continued growth of a proportion of the organisms and greater opportunities for the occurrence of mutants. For that reason, if for no other, inadequate dosage of the chosen antibiotic was to be condemned.

DR. T. J. CLAFFEY said that the work at Saint Vincent's Hospital had been started in 1951 with the main aim of finding, with the substance chloramphenicol, a method of getting rid, quickly and adequately, of wound infection when present, with the thought in mind that it might be a substance that would not produce resistant organisms as penicillin had done. That was in June, 1951. At that stage they treated a number of patients with chronic ulcers of the leg; but before treatment was started, swabs were taken and examined, and the sensitivity of the infecting organisms was determined to penicillin, streptomycin, aureomycin and "Chloromycetin". It was found that "Chloromycetin" was the only antibiotic to which the various organisms were universally sensitive. It had to be mentioned that the patients then treated were out-patients. They found that it was possible to sterilize or remove bacteria from the lesions within approximately forty-eight hours; the finding fascinated them. There was one proviso—to accomplish that, it was necessary to be able to get at the surface area of the lesion. There was a patient who had an infected wound from an incision for varicose veins. An incision up near the groin was infected and poured pus. An incision in the lower part of the leg was infected and also poured pus. The wound in the leg was open; in forty-eight hours the organisms had disappeared from the lower wound, but not from the upper wound, which resembled a sinus more than an ulcer. Dr. Claffey went on to say that they had not had great success in healing the ulcers; more factors were involved than the infecting organisms. At that time they did strike Monilia; it worried them, and they had not solved the problem yet. The investigation had been interrupted, and had been started again after a break of about four or five months. Dr. Claffey wondered whether the organisms floating about the out-patient department would have developed any resistance to "Chloromycetin", which they intended to use again. In the three weeks preceding the meeting Dr. Claffey had taken swabs from about 30 wounds in the out-patient department and had tested the organisms for sensitivity. Most of the wounds were infected by *Staphylococcus aureus*, coagulase-positive; not one had shown resistance to "Chloromycetin". Dr. Claffey did not know what conclusions to draw, but those were the facts. The conclusions that might be drawn from the very limited investigation were a little nebulous; but in view of the warning they had received at the meeting, he thought the investigation would have to proceed very carefully.

DR. R. B. C. STEVENSON said that one point had not been sufficiently stressed among the dangers, and that was the problem of acquired reaction to later doses of penicillin. In that respect he whole-heartedly endorsed the statement that antibiotics should not be used very freely. At the Women's Hospital, Crown Street, the habit had grown up of using antibiotics on a large scale in the treatment of any woman who had any obstetric manipulation, and the same applied on the gynæcological side. Some of the patients returned later with serious infections, necessitating further injections of antibiotics, and had severe reactions. The tendency now was to stop the wide use of antibiotics. When they were used, they were given in large doses. Referring to the problem of resistant types of organisms at the Royal Prince Alfred Hospital, Dr. Stevenson said that perhaps it could be solved by the adoption of Dr. Coppleson's suggestions, though Dr. Rountree had refuted his criticism. The only certain conclusion was that it might be safer to keep patients out of hospital.

DR. C. C. MCKELLAR said that he had a question to ask relating to acute hæmatogenous osteomyelitis. He wondered whether Dr. Thomson could tell him anything about penicillin resistance in cases in which the pus was collected in the operating theatre, and in which therefore there was no opportunity for cross-infection. Dr. McKellar had not yet found clinical resistance in such cases. He had yet to encounter a case of multiple and fatal osteomyelitis since the introduction of penicillin.

DR. W. E. FISHER asked Dr. Thomson whether he considered the correlation between laboratory and clinical resistance to be 100%.

Dr. Thomson, in reply to Dr. Coppleson, said that Dr. Coppleson had proved his (Dr. Thomson's) point; Dr. Coppleson had obviously been left with chloramphenicol as the only effective antibiotic. Dr. Coppleson had referred to the Royal Prince Alfred Hospital as a low-dosage hospital; but he had not mentioned the dosage used at Saint Vincent's Hospital. Dr. Thomson did not think that Dr. Claffey need be nervous about going on with his investigation; he should go on with it. It would be valuable if in about six months he could report his results, because it would appear that chloramphenicol-resistance "climb" had commenced. In reply to Dr. McKellar, Dr. Thomson said that in cases of osteomyelitis in which the patients were admitted to hospital with an established infection the organisms would probably be sensitive to penicillin. A statement would shortly appear in THE MEDICAL JOURNAL OF AUSTRALIA dealing with the use of antibiotics. In that statement there were two recommendations about the use of antibiotics in staphylococcal infections: (i) in general practice penicillin was given as the first choice; (ii) in hospital practice, aureomycin was given as the first choice. In reply to Dr. Fisher, Dr. Thomson said that the answer was "no".

Dr. Macdonald, from the chair, thanked the speakers for their papers and those who had entered into the discussion. He said that the picture was rather gloomy; but as a result of the papers and discussion, those present would think a great deal. If the speakers had stimulated them to do that, they should feel well pleased.

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

THE EMPLOYMENT OF CONVICTS IN HOSPITALS.[1]

Colonial Secretary's Office,
Sydney, January 2, 1834.

James Bowman, Esq.

Sir,

In reply to your letter of the 11th Ultimo requesting that the prisoner named in the margin (Chas CALLINGTON) may be appropriated as an attendant to the Sydney Hospital I am directed by the Governor to inform you that, as the man is not a medical practitioner but a Tailor, Instructions have been given for his appropriation accordingly—and to point out, with reference to my letter of this days date containing His Excellencys disallowance of the employment of Convicts of the Medical profession at any of the Hospitals, that he has no objection to such ordinary Prisoners of the Crown being assigned to the Hospitals as may be absolutely necessary for discharging the duties of nurses, wardsmen &c. but that he will not allow any convict, who by his former mode of life is supposed to be acquainted with the practice of Medicine to be appropriated to any of the Colonial Hospitals in future.

I have, &c.,
T. C. HARRINGTON.

[1] From the original in the Mitchell Library, Sydney.

Congress Notes.

AUSTRALASIAN MEDICAL CONGRESS (BRITISH MEDICAL ASSOCIATION).

THE Executive Committee of the Eighth Session of the Australasian Medical Congress (British Medical Association) to be held at Melbourne from August 22 to 29, 1952, has sent the following information.

PROGRAMME OF MEETINGS.

Plenary Sessions.

The programme for the plenary sessions of Congress to be held on August 26 and 27 (Tuesday and Wednesday) has already been mentioned; the details will be published in a subsequent issue.

Provisional Programme of Sectional Meetings.

Section of Anæsthesia.

Thursday, August 28:

Presidential address, "The Influence of Modern Methods Upon the Technique of Students", Dr. A. D. Lamphee (South Australia).

Combined Session with Section of Surgery.

"Resuscitation", Dr. E. Barclay Drevermann (Victoria), Dr. J. F. McCulloch (New South Wales), Dr. I. H. Cuming (Victoria).

"Hypotensives", Dr. R. H. Orton (Victoria).

"Thiopentone Sparing Compounds", Dr. L. T. Shea (New South Wales).

Friday, August 29:

Combined Session with Section of Oto-Rhino-Laryngology:

"Anæsthesia in Ear, Nose and Throat Surgery"—

"Local Anæsthesia in Ear, Nose and Throat Surgery", Dr. R. Palmerston Rundle (Queensland).

"General Anæsthesia in Ear, Nose and Throat Surgery", Dr. J. Ellis Gillespie (Victoria).

Museum meeting at Australian Society of Anæsthetists' Centre: "History of Regional Analgesia", Dr. Norman James (Victoria).

Section of Dermatology.

Thursday, August 28:

Presidential address, "Unusual Aspects of Cutaneous Neoplasms", Dr. H. M. Trethowan (Western Australia).

Combined Session with Section of Radiology (Radiotherapy), "Angiomata of the Skin".

Friday, August 29:

Three short papers on different aspects of common skin conditions—Dr. A. J. Day (Victoria), Dr. R. J. D. Turnbull (Tasmania), Dr. H. McMillan (Western Australia).

Section of History of Medicine.

Thursday, August 28:

Presidential address, "The History of the Australian Hospital Ships", Dr. A. S. Walker (New South Wales).

"Religio Medici", Dr. Colin Macdonald (Victoria).

"The History of Anatomical Illustration", Associate Professor Russell (Victoria).

"Memorable Year", Dr. F. E. Littlewood (Victoria).

"The Advent of Women into Medicine", Dr. Younger Ross (Victoria).

Friday, August 29:

"William Thomson and the History of the Contagionist Doctrine in Melbourne", Dr. B. Gandevia (Victoria).

"Sir James Mackenzie", Dr. M. Kelly (Victoria).

Section of Medicine.

Thursday, August 28:

Presidential address, "Medical Aspects of Mitral Valve Surgery", Dr. J. K. Maddox (New South Wales).

"Surgical Aspects of Mitral Valve Surgery", Dr. C. J. O. Brown (Victoria), Dr. F. H. Mills (New South Wales).

"Clinical Studies of Pancreatitis", Dr. E. Saint (from the Clinical Research Unit of the Walter and Eliza Hall Institute of Medical Research and Royal Melbourne Hospital).

"Early Diagnosis of Primary Bronchogenic Carcinoma", Dr. H. Maynard Rennie (New South Wales).

Combined Session with Section of Surgery and Section of Radiology (Radiodiagnosis).

"Management of the Complications of Peptic Ulcer", Dr. Avery Jones (United Kingdom), Dr. J. O'Sullivan (Victoria), Sir Gordon Gordon-Taylor (United Kingdom).

Friday, August 29:

"The Causes of Asthma", Dr. Charles Sutherland (Victoria).

"The Management of Acute Coronary Lesions", Dr. H. B. Kay (Victoria).

"Factors which Control the Fat Content of Liver Cells", Professor C. H. Best (Canada).

Combined Session with Section of Surgery and Section of Radiology (Radiotherapy).

"Management of Thyrotoxicosis", Dr. F. F. Rundle (New South Wales), Dr. W. P. Holman (Victoria), Dr. Keith Fairley (Victoria).

Section of Naval, Military and Air Force Medicine and Surgery.

Thursday, August 28:

Presidential address, "The Medical Considerations Concerning Enlistment in the Services", Major-General F. Kingsley Norris (Victoria). (Two short papers will be presented, one by a representative of the Royal Australian Naval Medical Service and one by a representative of the Royal Australian Air Force Medical Service. Arrangements have been made for members of the Section and other interested members of Congress to visit the Royal Australian Air Force Station at Point Cook on Monday, August 25, where matters in relation to service aspects of aviation medicine will be presented.)

Section of Neurology and Psychiatry.

Thursday, August 28:

Symposium, "Problems in Epilepsy and its Management". Opening comments, the President, Dr. H. M. Birch (South Australia): "Present-Day Concepts of Epilepsy", Dr. E. Graeme Robertson (Victoria); "Structural Pathology of Epilepsy", Dr. L. B. Cox (Victoria); "Queer Turns: The Lesser Known Manifestations of Epilepsy", Dr. John Williams (Victoria); "Drug Treatment of Epileptic Attacks", Dr. George Selby (New South Wales); "The Psychological and Social Management of the Epileptic", Dr. Guy Springthorpe (Victoria).

"Head Injury and Psychiatric Art with Reference to Leucotomy", Dr. Cunningham Dax (Victoria).

"Murray Valley Encephalitis: Neurological and Pathological Aspects", Dr. E. Graeme Robertson (Victoria).

"Enuresis and Parental Guidance", Professor J. Bostock (Queensland).

Friday, August 29:

"Congenital Vascular Deformations of the Brain", Dr. L. B. Cox (Victoria).

"The Thalamus and its Connexions", Professor LeGros Clark (United Kingdom).

Symposium, "Sedative Drugs, Their Uses and Abuses": "The Mode of Action of Sedatives", Dr. Hales Wilson (New South Wales); "Addiction to Sedatives", Professor W. S. Dawson (New South Wales); "Insomnia in General Practice", Dr. David Ross (New South Wales).

Symposium, "Alcohol": "Alcohol as a Social Problem", Dr. J. Hurt (Victoria); "The Neurological Aspects", Dr. J. J. Billings (Victoria); "The Management of the Alcoholic", Dr. A. J. Sinclair (Victoria).

"Temporal Lobe Syndromes", Dr. L. R. Rail (New South Wales).

"Temporal Lobe Tumours", Dr. J. Game (Victoria).

Section of Obstetrics and Gynæcology.

Thursday, August 28:

Combined Session with Section of Pædiatrics.

"Prematurity."

"Indications and Necessity of Induction with Special Reference to Fœtal Condition", Dr. W. F. Joynt (South Australia).

"Pathology of Premature Babies", Dr. M. Heseltine (New South Wales).

"Treatment", at home—Dr. J. Long (Victoria), in hospital—Dr. Kate Winning (New South Wales).
"Prognosis and End Results", Dr. Kate Campbell (Victoria).
"Early Detection of Cancer of the Cervix", Dr. M. J. Stening (New South Wales).
"Clinical Diagnosis of Vaginal Flora", Dr. W. W. Wilson (Tasmania).
Film—"Physiotherapy in Obstetrics", Dr. Grace Cuthbert (New South Wales).

Friday, August 29:

"Extraperitoneal Cæsarean Section and Film", Dr. G. Bearham (Victoria).

Combined Session with Section of Radiology.
"Review of 1000 Cases of Pelvimetry", Dr. Colin Macdonald (Victoria).

"Care of the Rhesus Negative Mother", Professor G. F. Gibberd (United Kingdom).
"Hæmorrhage during Ante-Natal Period", Dr. R. H. Nattrass (Western Australia).

Section of Ophthalmology.

(In conjunction with the Twelfth Annual Meeting of the Ophthalmological Society of Australia (British Medical Association.).)

Tuesday, August 26:

Presidential address, "Solar Retinitis", Dr. James Flynn (New South Wales).

Wednesday, August 27:

"Child's Guide to Fundus Oculi", Dr. John Foster (United Kingdom).

Thursday, August 28:

"The Changing Attitude to Developmental Anomalies", Professor Ida Mann (Western Australia).
"The Advantages of General Anæsthesia in Ophthalmology", Dr. T. Travers (Victoria).
"Our Present Concept of Primary Glaucoma", Dr. A. Reese (United States of America).
"The Budinger-Muller Lid Plastic Operation", Dr. John Foster (United Kingdom).
"The Ridley Lenticulus Operation", Dr. John Foster (United Kingdom).

Friday, August 29:

"Observations on the Eye of the Monotreme", Dr. K. J. O'Day (Victoria).
"Investigations into the Blood Supply of the Optic Nerve with Special Reference to the Papilla", Dr. John Bignell (Victoria).
"Curiosa Ophthalmica", Dr. John Foster (United Kingdom).
"Melanosis of the Conjunctiva", Dr. A. Reese (United States of America).
"Trends in Cataract Surgery", Dr. A. Reese (United States of America).
"Dacryorhinocystostomy", Dr. Boyd Law (New South Wales).

Section of Orthopædics and Physical Medicine.

Thursday, August 28:

Presidential address, "Medico-Legal Aspects of Orthopædic Practice", Dr. J. W. Van R. Hoets (New South Wales).
"Hip Arthroplasty", Dr. D. Rowe (New South Wales).
"Common Disorders of Cervical Spine", Dr. J. R. Barbour (South Australia).
"Brachial Neuritis" (thoracic outlet syndrome), Professor Lambert Rogers (United Kingdom), Dr. I. D. Miller (New South Wales), Dr. Charles Hembrow (Victoria).

Friday, August 29:

Combined Session with Section of Radiology.
"Demonstration of Orthopædic Procedures with X-Ray Control", Dr. Gwynne Villiers (Victoria), Dr. John Jens (Victoria).
"Rheumatoid Arthritis", Dr. M. Kelly (Victoria), Dr. L. J. A. Parr (New South Wales).
Clinical meeting at Frankston Orthopædic Hospital, Dr. Eric Price (Victoria), Dr. John Colquhoun (Victoria).

Section of Oto-Rhino-Laryngology.

Thursday, August 28:

Presidential address, "Cancer of the Larynx", Dr. R. M. Glynn (South Australia).
"Foreign Bodies in Food and Air Passages", Dr. E. A. Matison (South Australia).
"Clinical Studies in Œsophageal Obstruction in Childhood", Dr. R. V. Hennessy (Victoria).
"Fenestration": (i) "Observations on the Fenestration Operation", Dr. Stephen Suggit (Queensland); (ii) "Skin Grafts to Fenestration Cavities", Dr. A. B. K. Watkins (New South Wales).

Friday, August 29:

Combined Session with Section of Anæsthesia.
"Anæsthesia in Ear, Nose and Throat Surgery": "Local Anæsthesia in Ear, Nose and Throat Surgery", Dr. R. Palmerston Rundle (Queensland); "General Anæsthesia in Ear, Nose and Throat Surgery", Dr. J. Ellis Gillespie (Victoria).
"Alleviation of Deafness", Dr. G. Henderson (Western Australia).
"Dental Sepsis in Relation to Maxillary Infection", Dr. W. E. Fleming (Victoria).
"Statistical Survey of Antihistamines", Dr. R. H. O. Donald (Victoria).

Section of Pathology, Bacteriology, Biochemistry, Experimental Medicine and Forensic Medicine.

Thursday, August 28:

Presidential address, "The Role of the Laboratory in the Control of Antibiotic Therapy", Dr. Edgar Thomson (New South Wales).
"Hepatitis: Histological Diagnosis", Dr. J. Perry (Victoria).
"The Effect of Long-Continued Administration of Adrenaline upon the Carbohydrate Metabolism and Cardio-Vascular System of the Dog", Dr. D. M. Adams (New South Wales).
"Murray Valley Encephalitis."
"A Clinical Description of the 1951 Epidemic in Victoria", Dr. H. McLorinan (Victoria).
"An Encephalitis Virus Isolated in South Australia", Dr. J. A. R. Miles (South Australia).
"Laboratory Studies of the Victorian Virus", Mr. E. L. French, M.Sc. (Victoria).
"The Contrasting Epidemiological Picture in 1951 and 1952", Dr. S. G. Anderson (Victoria).
"Discussion of Preceding Papers", Sir Macfarlane Burnet (Victoria).

Friday, August 29:

"Time of Death", Dr. F. J. Cairns (New Zealand).
"Hæmolytic Anæmias", Dr. G. C. DeGruchy (Victoria).
Combined Session with Section of Public Health, Industrial Medicine, Tropical Medicine and Aviation Medicine.
"Leptospirosis in Victoria", Dr. W. J. Stevenson (Victoria), Dr. J. E. D. Lane (Victoria), Dr. A. Ferris (Victoria).

Section of Pædiatrics.

Thursday, August 28:

Combined Session with Section of Obstetrics and Gynæcology.
Symposium, "Prematurity": "Indications and Necessity of Induction with Special Reference to Fœtal Condition", Dr. W. F. Joynt (South Australia); "Pathology of Premature Babies", Dr. M. Heseltine (New South Wales); "Treatment", at home—Dr. J. Long (Victoria), in hospital—Dr. Kate Winning (New South Wales); "Prognosis and End Results", Dr. Kate Campbell (Victoria).
Symposium, "Acute Abdominal Pain in Infancy and Childhood": "The Problem of the Child in the Home", Dr. Charles Richardson (Victoria); "The Medical Problem", Dr. S. E. Robertson (New South Wales); "The Surgical Problem", Dr. Douglas McKay (South Australia).

Friday, August 29:

Symposium, "The Backward Child": "The Ætiology", Dr. F. Arden (Queensland); "Clinical Patterns", Dr. D. G. Hamilton (New South Wales); "The Management, Including Education of the Parents and Training of the Child", Dr. R. T. Binns (South Australia); "Mental Testing and Special Education Facilities", Dr. A. R. Phillips (Victoria).

"Hydrocephalus or Enlargement of the Head in Infancy and Childhood", Dr. R. S. Hooper (Victoria).
"Management of Hæmolytic Disease of the Newborn", Dr. E. Turner (Victoria).
"A Survey of Tuberculous Meningitis Treated with Streptomycin at the Royal Alexandra Hospital for Children", Dr. John Beveridge (New South Wales).
"Diagnosis of Anæmia in Childhood", Dr. John Colebatch (Victoria).

Section of Public Health, Industrial Medicine, Tropical Medicine and Aviation Medicine.

Thursday, August 28:

Presidential address, "Epidemiology of 'Q' Fevers" (Dr. Derrick's paper), Dr. A. Fryberg (Queensland).
"Epidemiology and Control of Leprosy", Dr. C. E. Cook (New South Wales).
"Lead Hazard in the Aviation Industry", Dr. F. S. Parle (Victoria).
"Human Engineering", Dr. J. C. Lane (Victoria).
"Problems in Immunization against Whooping-Cough", Dr. S. Fisher (Victoria).

Friday, August 29:

Session on Diarrhœa, Dr. F. W. Williams (Victoria), Dr. S. Ormerod (Victoria), Dr. V. Collins (Victoria).
Combined Session with Section of Pathology, Bacteriology, Biochemistry, Experimental Medicine and Forensic Medicine. "Leptospirosis in Victoria", Dr. W. J. Stevenson (Victoria), Dr. J. E. D. Lane (Victoria), Dr. A. Ferris (Victoria).

The Section of Naval, Military and Air Force Medicine and Surgery have arranged a visit to the Royal Australian Air Force Station at Point Cook on Monday, August 25, where matters in relation to Service aspects of aviation medicine will be presented.

Section of Radiology and Radiotherapy.

Thursday, August 28:

"Presidential address, "A Brief Review and Demonstration of the Interrelationship of Some of the Congenital Bone Dystrophies", Dr. H. R. Sear (New South Wales).
"Carcinoma of the Cervix", Dr. John Mayo (South Australia).
"Bronchiectasis", Dr. J. N. Burgess (Victoria).
Combined Session with Section of Dermatology.
"Angiomata of the Skin."
Combined Session with Sections of Medicine and Surgery.
"Management of the Complications of Peptic Ulcer", Dr. Avery Jones (United Kingdom), Dr. J. O'Sullivan (Victoria), Sir Gordon Gordon-Taylor (United Kingdom).

Friday, August 29:

Combined Session with Section of Orthopædics and Physical Medicine.
"Demonstration of Orthopædic Procedures with X-Ray Control", Dr. Gwynne Villiers (Victoria), Dr. John Jens (Victoria).
Combined Session with Section of Obstetrics and Gynæcology.
"A Preliminary Review of 1000 Cases of Pelvimetry", Dr. Colin Macdonald (Victoria).
Combined Session with Sections of Medicine and Surgery.
"Management of Thyrotoxicosis", Dr. F. F. Rundle (New South Wales), Dr. W. P. Holman (Victoria), Dr. Keith Fairley (Victoria).

Section of Surgery.

Thursday, August 28:

Presidential address, "Gall-Stones—No Cause for Complacency", Professor N. G. Sutton (Queensland).
Combined Session with Section of Anæsthesia.
"Resuscitation", Dr. E. Barclay Drevermann (Victoria), Dr. J. F. McCulloch (New South Wales), Dr. I. H. Cuming (Victoria).
Combined Session with Section of Medicine and Section of Radiology (Radiodiagnosis).
"Management of the Complications of Peptic Ulcer", Dr. Avery Jones (United Kingdom), Dr. J. O'Sullivan (Victoria), Sir Gordon Gordon-Taylor (United Kingdom).

Friday, August 29:

"Death due to Head Injury: Its Causes and Prevention", Dr. R. S. Hooper (Victoria).
"Management of Acute Retention", Dr. N. Bonnin (South Australia).
Combined Session with Section of Medicine and Section of Radiology (Radiotherapy).
"Management of Thyrotoxicosis", Dr. F. F. Rundle (New South Wales), Dr. W. P. Holman (Victoria), Dr. Keith Fairley (Victoria).

For further details of scientific sessions, see programme.

In addition, there will be the following displays during Congress week:

1. The Museum Committee has arranged a display in the Histology Department, first floor, Anatomy School.

2. An exhibition of doctors' hobbies will be held in the Geology School.

3. On Tuesday, August 26, Mr. Newman Rosenthal, B.A., B.Sc., Director of Visual Aids at the University of Melbourne, will give a lecture demonstration of the latest advances in visual aids as applied to medical practice, and an exhibition of visual aids (which will be open all day) has been arranged for Wednesday, August 27.

Films of general interest will be shown in the Union Theatre every day from 12 noon to 1 p.m. except on Wednesday, when a special Air Force film on "The Medical Effects of the Atom Bomb" will be screened. Films of special scientific interest will be shown after sectional meetings between 12 noon and 1 p.m. and 4 p.m. and 5 p.m. each day.

Congress Dinner.

The Congress dinner will be held at the Royale Ballroom, Exhibition Building, Melbourne, on the evening of Thursday, August 28, 1952. Members of Congress and their wives (or husbands) may attend, but as the number which can be accommodated is limited to 900, seating will be allotted strictly in accordance with priority of application. Evening dress with decorations will be worn, and, so far as possible, the wishes of guests with regard to seating will be met. It is expected that a contribution of three guineas per head will be necessary from those attending the dinner.

Correspondence.

LEPTOSPIROSIS IN AUSTRALIA.

SIR: The meeting of the Public Health Committee of the National Health and Medical Research Council, held in Sydney on May 19, 1952, was addressed by Dr. J. I. Tonge and Dr. I. Mackerras upon recent research into the incidence, distribution and economic importance of leptospirosis in Queensland.

Research in Queensland has shown not only that leptospiral infections are more frequent and more widely dispersed than was formerly supposed, but also that new and hitherto unidentified strains of leptospiræ are involved.

A report from the committee was subsequently considered by the National Health and Medical Research Council. The Council, after discussion, decided that the practising profession in Australia should be warned of the widespread distribution of leptospirosis and asked to cooperate in the study of pyrexias of unknown origin in order that the actual incidence of leptospiral strains in Australia might be more accurately determined.

For this purpose, it is suggested that medical practitioners should send, for examination in State health laboratories or the School of Public Health and Tropical Medicine, specimens of sera from patients suffering from obscure pyrexias.

The active cooperation of medical practitioners in this respect will be valued by both State and Commonwealth health authorities, and may well lead to the precise identification and appropriate treatment of a proportion of cases of leptospirosis at present unsuspected in many widely separated parts of Australia.

Yours, etc.,
A. J. METCALFE,
Chairman, National Health and Medical Research Council.

Canberra, A.C.T.,
June 6, 1952.

NASAL SINUSITIS.

SIR: The views expressed by Dr. Harry Windsor (THE MEDICAL JOURNAL OF AUSTRALIA, May 31, 1952) coincide with my own to a large extent. However, it should be made clear, since he refers to my earlier letter to you, that the subject of his communication is quite different from that of mine. The patient about whom I wrote did not have a bronchiectasis, although the radiologist had referred to this word as a thought that had occurred to him. She did not

suffer from a chronic sinusitis, nor did I propose that she should undergo any kind of radical operation.

It is worth stating clearly, not for the first time, that there are two different methods of operating on the maxillary antrum and that the methods differ both in principle and object. They are not interchangeable. It is the selection of the wrong operation on so many occasions and the unjustified prophecies of complete cure which are the reasons for widespread dissatisfaction with antrum surgery.

If the patient's trouble is a recurrent antritis with blockage of the natural ostium, which occurs so often in the vasomotor and allergic kind of nasal disease, the simple antrostomy is a beneficial and rewarding procedure. Coupled with suitable medication it is all that is required by such patients, nor do they need a lot of after-treatment, lavage *et cetera*.

When there is really chronic infective antral disease, and the mucosal lining has become pus-forming and has undergone permanent changes, it is necessary to remove this membrane. In such a case the radical type of operation is needed.

What Dr. Windsor says is quite true—the operation on the antrum will not cure the bronchiectasis; but nobody would expect it to do so. The fact that a coughing patient reinfects his antrum is too well established to argue about. Nevertheless, the patient with a chronic suppurating antrum is benefited by having the pyogenic membrane removed, and many have been so improved. One important gain is the diminished risk of the intranasal infection causing intracranial complications.

Yours, etc.,

193 Macquarie Street,
Sydney,
June 2, 1952.

ERIC P. BLASHKI.

PAINLESS CHILDBIRTH, AND THE IMPORTANCE OF BEING EARNEST.

SIR: Nowadays the young doctor starting in practice is in danger of failing to give to all of his obstetric patients the benefits of the principles laid down by Dr. Grantly Dick Read. The large public hospitals have developed ancillary departments staffed by lecturers and physiotherapists. The young doctor as assistant, or in his own practice, is apt to be overwhelmed by this, and limit himself to advising the new midwifery case who books up with him to read one of the books on the subject. It is my experience that this is not enough—the spoken word is essential. A printed slip given out at about the seventh month was only moderately effective, but a talk at near the seventh month with the patient lying on the examination table has brought satisfying results.

The wording varies slightly according to the intelligence of the patient, but the main points are made in such a way as this:

> It's about time we had a few words about this business of painless childbirth. You've been reading about it I suppose. Well, I'll tell you my ideas. The whole idea is to get it out of your head that you go into labour. You don't go into labour at all—you go into relaxation. . . . The more you labour the more you hold up the works.
>
> Now at the present time the exit of your womb, called your cervix, is a knot about as big as the end of my thumb. The mouth of the cervix or womb is so small that it would just admit a crochet needle. Ninety per cent. of the time you are having the baby is spent pulling this out sideways until it's big enough for a baby's head to come through. Nothing you can do can help this. Everything you do holds it up. It's done by means of contractions. Theoretically, if you can remain perfectly relaxed when a contraction occurs it is painless. If you push down or tighten yourself down below, or get frightened and tense yourself, you turn what should be a painless contraction into a "pain".
>
> It's a good thing to remember that you can do nothing to help; that your womb would get the job over quicker if it were alone in the next room completely dissociated from you.
>
> When the cervix is completely dilated your waters break. The birth canal is now opened up ready for the baby's head to come through. For this last stage you can help by pushing if you like: but it doesn't matter if you do or not.

This explanation takes less than three minutes. The sentences follow each other with plenty of pauses. One must beware of allowing repetition to dull the air of earnest conviction necessary for each patient.

This talk is followed by a demonstration of a good way to relax the abdominal muscles, that is, open the mouth, relax the jaw and slowly take little breaths in and long calm sighs out. She is advised to practise this relaxation exercise twice a day for ten minutes lying on a bed at home with one hand resting on the abdomen. She should practise till head, shoulders, back, buttocks, thighs and legs feel as if they could fall through the bed. When good enough at this, she is told to imagine a contraction is coming and start up the little breaths in and long slow breaths out. "You have to get so good at it that you can keep it up when strange things begin happening in your abdomen."

This whole explanation takes five or six minutes. It becomes automatic to ask at subsequent visits if they are practising their breathing exercises and to show you how. Highly strung types may huff and puff, and have to be shown that it is a gentle breath in and a gentle long slow sigh out.

This method obviously breaks down unless the sisters at the maternity hospitals involved believe the same as you do. I have yet to meet an uncooperative nurse, providing an explanation such as this is made and a breathing demonstration given.

The hardest cases to handle are probably the persistent occipito-posterior *primiparæ* with early rupture of membranes and weak contractions, coming into labour for a few hours and going off again. I make it a point to be quickly on the scene to quieten their fears. They readily understand an explanation that the baby's head is coming down back to front, and it cannot be born that way, that Nature will take an awful lot of time turning it round the right way, but they will just have to be patient and everything will be all right in the end.

Curiously the expected three or four day case is often over in two days—the mother maybe looking as "fresh as a daisy".

God bless Grantly Dick Read. He has cast out fear.

Yours, etc.,

23 Douglas Parade,
Williamstown, W.16,
Melbourne.
May 27, 1952.

LEO J. GURRY.

EPISTAXIS AND SINUS INFECTION.

SIR: In the journal for June 7, 1952, page 793 ("Abstracts from Medical Literature"), appears an extract from an article by I. J. L. Morris on epistaxis and sinus infection.

I sent to the journal an article written on September 6, 1950, entitled "Sinus Epistaxis" and which subsequently appeared in your journal.

This was possibly the first published article giving a description of this phenomenon, which I had observed for some years. I gave some, in my opinion, interesting and instructive case histories.

I would like to once more stress certain points. The great majority of cases of sinus epistaxis, probably, are self-limiting and are not recognized as such. But the condition may have serious and even fatal results.

I gave a brief description of the sinus mucosa, which in the severe cases is thickened and intensely congested, due, I believe, to infection with a hæmolytic streptococcus; the mucosa bleeds very freely on the slightest touch, hence the procedure of antral lavage itself may precipitate a severe hæmorrhage, as in cases described.

Prior to the use of antibiotics, the only satisfactory method of dealing with severe cases was to remove the mucosa at fault, that is, to employ radical surgery.

In the last few years, however, I have learned that the early and efficient administration of penicillin will stop the hæmorrhage by overcoming the infection which is causing it. Incidentally, in sinus surgery and the like, the coincidental administration of penicillin practically eliminates those unpleasant sequelæ, "reactionary" and secondary hæmorrhage.

The time is not far distant when the operation of lobectomy for bronchiectasis, antral lavage and more radical surgery for sinus disease (except in conditions caused by trauma, foreign bodies, such as a tooth in an antrum, *et*

cetera) will be an admission that the diseases were not recognized in their early stages nor the patient properly cared for. Nasal accessory sinus disease (except traumatic cases already referred to, some specific diseases and perhaps newgrowths) and bronchiectasis are the same condition in different sites, commonly, if not always, in the same patient, though the degree of development of the condition in different sites varies enormously. The conditions are congenital in origin, and the great majority of such cases are overlooked until a severe superadded infection occurs.

The prime cause is a biochemical one, which may result in many other manifestations, such as Ménière's syndrome, migraine, some epilepsies, gastro-intestinal upsets *et cetera*, and, of course, the many recognized and so-called "allergic" conditions.

With regard to this biochemical dysfunction, the out-patient department of a hospital for sick children affords abundant evidence of the facts as I have stated them, but frequently it is very time-consuming to get a proper history of the patient and the family history.

These conditions in children can often be diagnosed before physical signs or X rays reveal them. Time and again the worried mother has been told, after X ray *et cetera*, that "the lungs are all right", only to find out as the years go by that symptoms get worse and definite signs become only too obvious.

As the late Dr. Camac Wilkinson used to tell his students in Sydney, "the doctor who waits for physical signs to develop before he diagnoses pulmonary tuberculosis will next be writing the death certificate"; similarly, in these cases of biochemical dysfunction, leading to nasal sinus disease, bronchiectasis *et cetera*, the doctor who waits for physical signs to develop before making the diagnosis will next be recommending radical sinus surgery, pulmonary lobectomy *et cetera*.

Surgical measures, various electrical treatments *et cetera* are not dealing with the real disease, but only with what should be preventible secondary conditions.

Yours, etc.,

Southport, Queensland, June 9, 1952. ERNEST CULPIN.

TREATMENT OF RHEUMATOID AND OSTEO-ARTHRITIS BY SODIUM PARA-AMINO-SALICYLATE WITH PRESENTATION OF CASES.

SIR: I was interested to read the article entitled "Treatment of Rheumatoid and Osteoarthritis by Sodium Para-aminosalicylate with Presentation of Cases" by Michel Brous which appeared in THE MEDICAL JOURNAL OF AUSTRALIA, Volume I, 1952, page 774.

I would like to commend Dr. Brous on his use of PAS in the treatment of these conditions. Investigations have been carried out over the past two years by myself in respect to the mode of action of PAS against tuberculosis. It does appear from these investigations that a fundamental mode of action may be through the adrenal system, and that it acts as a replacement therapy for a deficiency associated with the disease tuberculosis itself.

Hetzel and Hine (*The Lancet*, July 21, 1951, page 94) deduced that the therapeutic effect of salicylates was mediated by the pituitary and suprarenal glands. My investigations have shown the close correlation of the action of salicylates, cortisone and PAS in the treatment of acute rheumatic fever, rheumatoid arthritis and tuberculosis respectively. The results of blood sedimentation rate investigations during therapy have all followed a similar pattern.

Side effects in the use of these three drugs have been very similar, and these have included upsets of electrolytic balance, glycosuria and various endocrine dysfunctions.

The withdrawal of cortisone, following treatment in the presence of tuberculosis and rheumatoid arthritis, usually results in a flare-up of the condition, and this also occurs frequently following withdrawal of salicylates and PAS in acute rheumatic fever and in active tuberculosis respectively.

It has seemed that the action of these drugs is closely related, and that these three diseases also may be in some ways more closely allied than generally considered. If this is so, the beneficial effect of PAS used in osteoarthritis and rheumatoid arthritis may well be the result of rational therapy.

It would be interesting, however, to review the progress of these patients some months after cessation of PAS treatment.

Yours, etc.,

Adelaide, June 12, 1952. R. MUNRO FORD.

SUBACUTE BACTERIAL ENDOCARDITIS CAUSED BY ERYSIPELOTHRIX RHUSIOPATHIÆ.

SIR: With reference to Dr. Bauer's letter of May 24, 1952, it is very gratifying to know that he is so far advanced in modern cardiology that he can make the following extract from Paul Dudley White's book, "Heart Disease" (1951), look so incredibly out of date. Referring to the symptoms of subacute bacterial endocarditis, he says: "The gradual, insidious onset of this disease often prevents any exact determination of the time of its beginning. There may be a feeling of increasing fatigue and loss of appetite, vague joint and muscle pains; the victim may appear pale, listless and 'run down' for a few weeks before fever or other symptoms force him to bed. Months sometimes elapse with no definite idea of what is wrong. Usually, however, in the early weeks of the illness the temperature reaction, anæmia, enlarged spleen or clubbing of the fingers and heart signs and blood culture show the presence of this serious illness."

If this description is merely historical it is a great pity that it was published in 1951 as a modern description of symptoms, or has the author merely portrayed the diagnostic ineptitude of some simple, unenlightened practitioner, who allows months to elapse before he calls in a modern cardiologist?

I would like to thank Dr. Lawes very much for his letter. One appreciates the fact that no one today would hesitate to use antibiotics in large doses in any septicæmia with a temperature and with or without signs of previous cardiac disease, but one might hesitate to make the diagnosis of subacute bacterial endocarditis. I take it that the diagnosis of patent interventricular septum was missed on the patient's first admission to hospital with rheumatic fever in 1945.

Yours, etc.,

77 York Street, Sydney, June 11, 1952. W. E. DAVID.

ACQUIRED MELANOSIS: A GRAVE WARNING.

SIR: I would like to express my appreciation of the report by Dr. V. J. Kinsella, "Acquired Melanosis: A Grave Warning", THE MEDICAL JOURNAL OF AUSTRALIA, June 7, 1952.

I have not the slightest doubt that Dr. Kinsella's patient, Mr. K.R., was the gentleman who consulted me on March 22, 1949. I found in my records a sketch which is a copy of the Figure I on page 781. My clinical diagnosis was: melano-epithelioma with circumscribed melanosis; metastases in left axillary glands. No suggestion of histological examination was made. The diagnosis was self-evident.

I dutifully informed his local doctor and his daughter-in-law about the grave prognosis and urged them to refer the patient to a surgeon.

I wish to recall that already Hutchinson (1866) has described a condition since known as a "melanotic whitlow". The melanotic tumours with a circumscribed melanosis are familiar to all dermatologists. Infrequent, however, are cases with diffuse melanosis, that is, diffuse pigmentation accompanying metastases of a malignant melanoma. In a case I had the opportunity to observe there was a uniform dusky pigmentation of the skin and mucous membranes imitating in the beginning argyria and causing later complete blackening of the skin like in Addison's disease. Melanin was also present in urine. No malignant cells were discovered in the diffusely pigmented skin.

Yours, etc.,

Sydney, June 12, 1952. F. GOLDSCHLAG.

Medical Prizes.

THE STAWELL PRIZE.

THE Stawell Prize, a memorial to Sir Richard Stawell, is open for competition. The amount of the prize is £30.

The conditions are as follows:

1. The prize shall be awarded to the writer of the essay adjudged to be the best on a subject selected annually.
2. The subject for 1952 is "Peripheral Vascular Disease".
3. The dissertation should be based on personal observation and experience of the writer.
4. The competition is open to graduates of any Australian university.
5. The trustees reserve the right to withhold the award.
6. Essays must be delivered to the Medical Secretary, British Medical Association (Victorian Branch), by 4 p.m. on March 31, 1953.
7. Each essay must be typewritten or printed and must not exceed 75,000 words in length.
8. Each essay must be distinguished by a motto and must be accompanied by a sealed envelope marked by the same motto, containing the name and address of the author.
9. The trustees reserve the right to publish the prize essay.

Congresses.

INTERNATIONAL PHYSIOLOGICAL CONGRESS, 1953.

THE nineteenth International Physiological Congress will be held in Montreal from August 31 to September 4, 1953. All inquiries for detailed information should be addressed to Miss Margaret W. MacCallum, Executive Secretary, Room 426, Donner Building, McGill University, Montreal, Canada. The closing date for applications for enrolment is May 31, 1953. It is hoped that brochures and application forms will also be available at the meeting of the Australian and New Zealand Association for the Advancement of Science in Sydney.

Notice.

SECTION OF PREVENTIVE MEDICINE, VICTORIAN BRANCH OF THE BRITISH MEDICAL ASSOCIATION.

THE next meeting of the Section of Preventive Medicine of the Victorian Branch of the British Medical Association will be held in the Medical Society Hall, 426 Albert Street, East Melbourne, at 4.30 p.m. on Thursday, July 10, 1952. Dr. E. Cunningham Dax, Chairman of the Mental Hygiene Authority, will give an address on mental hygiene in relation to public health. All members of the Branch are invited to be present.

Obituary.

FRANCIS JOHN NIALL.

WE have received from Dr. J. G. Hayden the following appreciation of the late Dr. Francis John Niall.

Dr. Frank Niall was a friend of mine for twenty-five years and I would like to join with Dr. Kevin Rush in paying tribute to his memory. He was a man of high character, a loyal friend and a devoted husband and father. My association with him commenced when he was appointed to the staff at Saint Vincent's Hospital, and our interests in medicine being similar we had very much in common. He was a most able clinician with an extremely sound approach to the problems of diagnosis and treatment, a first-class teacher, a man of mature judgement and scrupulous integrity. I regarded him as one of our best physicians. His talents naturally led him to take a prominent part in the work of the clinical school, of which he was appointed dean in 1944; and during the war years, despite his large private practice, he gave unstintingly of his time in the

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED MAY 31, 1952.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	..	..	..	..	..	..	..	..	..
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	..	..	..	..	..	..	..	..	..
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	1	..	..	..	1
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	..	..	5(5)	..	..	..	1	..	6
Diphtheria	6(3)	2(2)	10(7)	..	2(2)	..	..	..	20
Dysentery (Bacillary)	..	..	14(13)	1(1)	13(10)	..	1	..	29
Encephalitis	..	..	..	..	..	..	..	..	..
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	..	..	..	..	13(4)	..	..	..	18
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	5	..	..	..	..	..	5
Malaria	..	..	1	..	..	..	..	..	1
Meningococcal Infection	2(2)	4(2)	1	1(1)	..	..	..	..	8
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	5(3)	1(1)	1	13(7)	1(1)	..	..	..	21
Puerperal Fever	..	..	2	..	..	..	..	..	2
Rubella	..	2(2)	..	..	1(1)	..	..	..	3
Salmonella Infection	..	1(1)	..	..	1	..	..	..	2
Scarlet Fever	17(8)	28(12)	1(1)	4(4)	..	2(1)	..	..	52
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	1(1)	..	..	..	..	..	1
Trachoma	..	..	..	..	..	..	..	..	..
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	37(32)	18(9)	18(14)	7(4)	12(7)	1	..	..	88
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	1(1)	..	..	..	1
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

interests of the hospital. He was an excellent administrator and a first-class committee man, who never wasted time on non-essentials, but clearly saw the major problem involved and devoted his discussion to that alone. He was one of the best examiners that I have encountered, and his judgement was never swayed by extraneous circumstances. For many years he was a university examiner for the final M.B., B.S. examinations and also examined for the degree of M.D.; in addition he occasionally examined for the membership of The Royal Australasian College of Physicians, of which he was a Foundation Fellow and at one time Honorary Secretary of the Victorian State Committee.

His death will be keenly felt by his friends, and Victorian medicine has suffered a great loss.

HENRY DOUGLAS STEPHENS.

We regret to announce the death of Dr. Henry Douglas Stephens, which occurred on June 17, 1952, at Melbourne, Victoria.

Australian Medical Board Proceedings.

NEW SOUTH WALES.

The following have been registered, pursuant to the provisions of the *Medical Practitioners Act*, 1938-1950, of New South Wales, as duly qualified medical practitioners:

Wade, Eric Arnold, M.B., B.S., 1952 (Univ. Sydney); Wallace, Gilbert Hugh Murray, M.B., B.S., 1952 (Univ. Sydney); Walters, Peter, M.B., B.S., 1952 (Univ. Sydney); Wells, John Graham, M.B., B.S., 1952 (Univ. Sydney); White, Bruce, M.B., B.S., 1952 (Univ. Sydney); White, Francis David, M.B., B.S., 1952 (Univ. Sydney); White, Rosalie Judith, M.B., B.S., 1952 (Univ. Sydney); Whiteway, Donald Wallace, M.B., B.S., 1952 (Univ. Sydney); Willcocks, Richard, M.B., B.S., 1952 (Univ. Sydney); Williams, Earle John, M.B., B.S., 1952 (Univ. Sydney); Williams, Lorna Letitia, M.B., B.S., 1952 (Univ. Sydney); Windon, Helen Margaret, M.B., B.S., 1952 (Univ. Sydney); Winn, Richard William, M.B., B.S., 1952 (Univ. Sydney); Woods, David Robert, M.B., B.S., 1952 (Univ. Sydney); Wright-Short, Frederick William, M.B., B.S., 1952 (Univ. Sydney).

Nominations and Elections.

The undermentioned have applied for election as members of the South Australian Branch of the British Medical Association:

Drever, Ian Campbell, M.B., B.S., 1951 (Univ. Adelaide) (qualified December, 1950), Angaston.

Shea, Brian Joseph, M.B., B.S., 1951 (Univ. Adelaide) (qualified December, 1950), 18 Greenhill Road, Dulwich.

Davenport, John, M.B., B.S., 1952 (Univ. Adelaide) (qualified December, 1951), 12 Northumberland Street, Heathpool.

The undermentioned have been elected as members of the South Australian Branch of the British Medical Association: Morgan, Owen Brakspear, M.B., B.S., 1952 (Univ. Adelaide) (qualified December, 1951); Moncreiff, Rostrevor Brooke, M.B., B.S., 1952 (Univ. Adelaide) (qualified December, 1951); Bell, Franklyn Gilbert, M.B., B.S., 1950 (Univ. Adelaide) (qualified December, 1949); Morey, Harry Francis, M.B., B.S., 1947 (Univ. Sydney).

The undermentioned have been elected as members of the New South Wales Branch of the British Medical Association: Boyd, Brian Anthony Majella, M.B., B.S., 1952 (Univ. Sydney); Bradley, Edgar David, M.B., B.S., 1951 (Univ. Sydney); Cahalan, Bernard Joseph Seymour, M.B., B.S., 1952 (Univ. Sydney); Donovan, John Kenmore, M.B., B.S., 1952 (Univ. Sydney); Hagan, Brian Elwin, M.B., B.S., 1951 (Univ. Sydney); Hardy Barker, Eric Edwin (provisional registration), M.B., 1952 (Univ. Sydney); Kiely, Philip Edmund, M.B., B.S., 1952 (Univ. Sydney); Musgrove, John Dennison (provisional registration), M.B., 1952 (Univ. Sydney); O'Neill, John Patrick, M.B., B.S., 1948 (Univ. Sydney); Pierce, Betty Ellen, M.B., B.S., 1952 (Univ. Sydney); Powell, Frederick Arbouin, M.B., B.S., 1945 (Univ. Sydney); Rogers, Elizabeth Mary, M.B., B.S., 1952 (Univ. Sydney); Shepherd, Alan Richard, M.B., B.S., 1952 (Univ. Sydney); Stacey, Noel Harrison (provisional registration), M.B., 1952 (Univ. Sydney); Stewart, Freda Mary, M.B., B.S., 1936 (Univ. Sydney); Wilson, Keith John, M.B., B.S., 1951 (Univ. Adelaide).

Diary for the Month.

JULY 1.—New South Wales Branch, B.M.A.: Council Quarterly.
JULY 2.—Western Australian Branch, B.M.A.: Council Meeting.
JULY 4.—Queensland Branch, B.M.A.: Branch Meeting.
JULY 8.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
JULY 8.—New South Wales Branch, B.M.A.: Organization and Science Committee.
JULY 11.—Queensland Branch, B.M.A.: Council Meeting.
JULY 14.—Victorian Branch, B.M.A.: Finance Subcommittee Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federal Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

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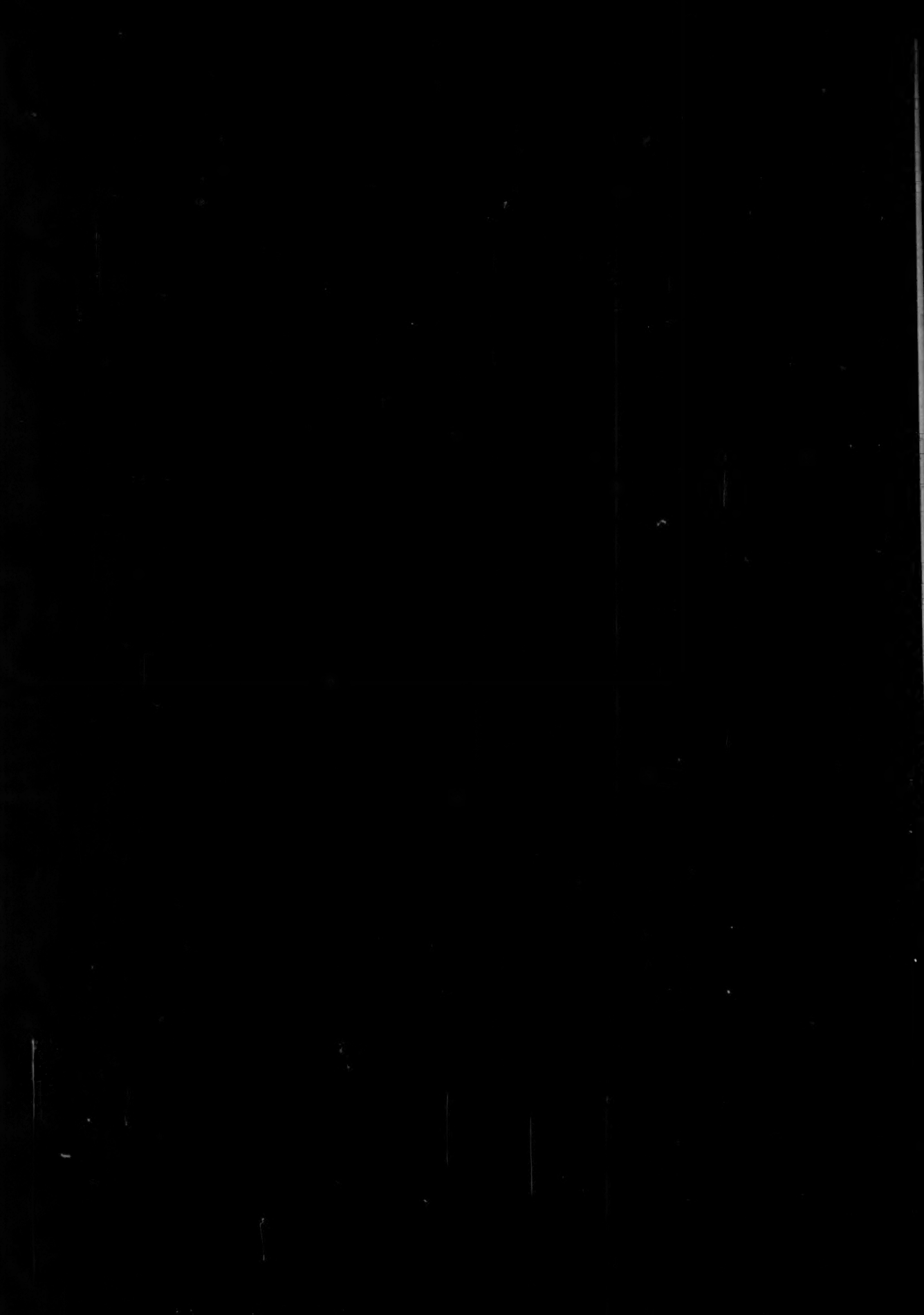

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AREEBA HOSPITALS BOARD, MAREEBA, NORTH QUEENSLAND.

PPLICATIONS are invited for position of Resident Medical er to commence duty on or 14th July, 1952. Duties con- of visiting small auxiliary hos- and out-patient clinics, in ion to general duties at reeba Hospital. Travelling ex- es allowed.

alary £874 10s. p.a. if without pital experience and £974 10s. r one year's hospital experience, basic wage adjustment (at ent £57 p.a.) and northern wance, £48 p.a., with free board, ing and laundry if single, or p.a. living-out allowance if ried (no married quarters ilable at hospital). Four weeks' annual leave.

Apply to Secretary, P.O. Box Mareeba, North Queensland, ting age, married or single, alifications and date available duty.

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Unopposed practice. Well staffed. l equipped, 23-bed hospital at posal. £1500 income guaranteed h allowances for weekly trips adjacent towns. Excellent mate. House with surgery to t. Electricity. For further par- ulars apply No. 783, c.o. this ce.

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Diploma in Anæsthetics; Diploma Psychological Medicine; Diploma Ophthalmology; Diploma in diology; Diploma in Laryn- gy; Diploma in Child Health; R.C.S.Eng., and all Surgical Ex- inations; M.R.C.P.Lond., and Medical Examinations; M.D. ses of all Universities; Courses all Qualifying Examinations. mplete guide to Medical Examin- ons sent free on application. pplicants should state in which alification they are interested. dress: Secretary, Medical Cor- pondence College, 19 Welbeck London, W.1.

VACANCY FOR MEDICAL SUPERINTENDENT OF MENTAL HOSPITAL, SUNBURY, VICTORIA.

APPLICATIONS (to be in the hands of the Chairman, Mental Hygiene Authority, 300 Queen Street, Melbourne, not later than 11/7/52) are invited for the above-mentioned position.

Salary per annum (gross): £1824 (minimum) to £1924 (maximum). (This includes a cost-of-living allowance, at present £324 per annum, less a deduction of approximately 10% of total emoluments for residence, fuel, light, vegetables, milk, laundry, etc.)

Successful applicant will be required to contribute to the Victorian Government Superannuation Fund, and would be eligible for long-service leave.

Duties: To be responsible, under the direction of the Authority, for the control and administration of the hospital mentioned. Opportunities for teaching and out-patient work will be made available.

Qualifications: Possession of a Diploma of Psychological Medicine (or higher medical qualification) or membership in the Australasian Association of Psychiatrists is essential.

Experience in hospital administration and psychiatry and the ability to teach and lecture.

VACANCY FOR RESIDENT MEDICAL OFFICER, MENTAL HOSPITAL, ARARAT, VICTORIA.

APPLICATIONS (to be in the hands of the Chairman, Mental Hygiene Authority, 300 Queen Street, Melbourne, not later than 11/7/52) are invited for the above-mentioned position. Statement of experience and qualifications and copies of two recent testimonials should accompany the application.

Salary per annum (gross): £1324 (minimum), £1574 (maximum) (annual increments of £50). This includes a cost-of-living allowance, at present £324 per annum, less a deduction of approximately 10% of total emoluments for residence (a separate house on the Reserve), fuel, light, vegetables, milk, laundry, etc.

Successful applicant will be required to contribute to the Victorian Government Superannuation Fund and would be eligible for long-service leave. As soon as practicable, the appointee would be transferred to the metropolis, if he desires to acquire the D.P.M. Further particulars will be supplied on application.

Duties: Under the control and direction of the Medical Superintendent to carry out the duties of a Resident Medical Officer.

QUEENSLAND INSTITUTE OF MEDICAL RESEARCH.

APPLICATIONS are invited from medical graduates for a Senior Research Fellowship. Tenure initially for one year, and may be renewable annually up to maximum of five years. Salary £1316 10s. to £1496 10s. per annum together with extra cost-of-living allowance of £25 per annum, commencing salary within this range depending upon qualifications and experience. Successful applicant will be stationed at the Institute's Field Station, Innisfail, North Queensland. Local transport will be provided. Duties consist of clinical and laboratory investigations into unidentified fevers. Knowledge of clinical pathology and laboratory methods desirable. Staff of the Field Station includes a bacteriologist.

Applications, including names of two referees, close with the Director, Queensland Institute of Medical Research, Herston Road, Valley, Brisbane, on 14th July, 1952. Copies of not more than three testimonials may be attached. Further information obtainable from the Director.

ROYAL PRINCE ALFRED HOSPITAL, CAMPERDOWN, N.S.W.

APPLICATIONS are invited for the position of Honorary Medical Officer for Venereal Diseases. Official application forms available from the Secretary. Applications close 28th July, 1952.—H. SELLE, General Superintendent.

ATHERTON HOSPITALS BOARD, QUEENSLAND.

APPLICATIONS are invited for the position of Medical Superintendent to the Atherton Hospital, North Queensland.

Salary classification: Minimum £1345, maximum £1595, plus basic wage adjustment of £106 per annum and sustenance allowance of £48, together with a modern unfurnished residence, fuel and light. (The residence available is well furnished, and a reasonable charge will be made for the use of this furniture.)

Appointee may be paid a commencing salary greater than the minimum stated, according to his experience. No right of private practice is allowed.

Daily average of in-patients 70, out-patients 50, at Atherton.

Two resident medical officers are employed.

Applications, with copies of references and details of military service, if any, should be forwarded to reach the undersigned on or before the 8th July, 1952.

Applicants are advised to use air mail post. Successful applicant will be required to take up duties in mid-August, 1952.

Apply W. H. SHERRIN, Secretary.

SNOWY MOUNTAINS HYDRO-ELECTRIC AUTHORITY, COOMA, N.S.W.

APPLICATIONS are invited for appointment with the Authority as Industrial Medical Officer.

Salary: £1268-£1758 per annum, subject to future cost-of-living adjustments as applicable in the Commonwealth Service. Commencing salary will be determined according to the qualifications and experience of the successful applicant.

Qualifications: Registered medical practitioner with at least three years' experience as such. Diploma of Public Health and experience in industrial medical work are desirable but not essential.

Duties: Responsible to the Chief Administrative Officer for the supervision of the Authority's medical services, including advice to the Authority on medical matters generally, accident prevention, industrial health hazards, and on procurement of medical stores and equipment. Medical examination of employees. Immediate treatment of medical and surgical emergencies.

The headquarters of the Authority are at Cooma, New South Wales, where the Industrial Medical Officer will be required to reside. A residence will be available on a rental basis within two months of appointment.

Each applicant should state his age, nationality, present position and salary and give full details of his academic qualifications and experience. Applications, closing on July 5, 1952, should be addressed to the Acting Secretary, Snowy Mountains Hydro-Electric Authority, Box 32, P.O., Cooma, New South Wales.

FLYING DOCTOR SERVICE OF AUSTRALIA.

APPLICATIONS are invited for the position of Flying Doctor at the Broken Hill Base administered by the N.S.W. Section of the Flying Doctor Service of Australia. Salary payable commensurate with experience, but not less than £1200 per annum, with furnished home provided. Applicants should state age, experience, marital state, war service (if any), and furnish the names of two persons for reference. The successful applicant will be expected to take up duties towards the middle of July, 1952. Applications should be addressed in writing to the Secretary, Flying Doctor Service of Australia (N.S.W. Section), 27 Hunter Street, Sydney.

THE WOMEN'S HOSPITAL, CROWN STREET, SYDNEY, N.S.W.

MEDICAL SUPERINTENDENT.

APPLICATIONS are invited, to be addressed to the undersigned, closing 25th July, 1952, for appointment as Medical Superintendent at a commencing salary of £1570 p.a. plus board and residence (subject to basic wage adjustments). Applicants to set out details of qualifications and experience, and to indicate when duties can be commenced (commencement of duties in early September if possible). Applicants required to enter into an agreement for a term of three years. Further particulars from R. B. GOLSBY, Secretary and Chief Executive Officer.

FOR SALE, X-Ray Unit, Mobile Floor Model, 35 kv., 30 ma., with extras. Perfect order. 'Phone M 6196 (Sydney).

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